(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 810 209 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
05.06.2002 Bulletin 2002/23

(21) Application number: **97113434.1**

(22) Date of filing: **24.08.1993**

(51) Int Cl.[7]: **C07C 311/13**, C07C 311/18, C07C 311/20, C07C 311/29, C07C 311/39, C07C 311/46, C07C 317/14, C07C 323/25, C07C 323/67, C07D 213/30, C07D 213/81, C07D 213/82, C07D 213/89, C07D 239/26, C07D 333/34, C07K 5/062, A61K 31/18, A61K 31/325

(54) **Alpha - and beta-amino acid hydroxyethylamino sulfonamides useful as retroviral protease inhibitors**

Hydroxyethylaminosulfonamide verwendbar als Inhibitoren retroviraler Proteasen

Sulfamides d'hydroxyéthylamino utiles comme inhibiteurs de protéases rétrovirales

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **25.08.1992 US 934984**

(43) Date of publication of application:
03.12.1997 Bulletin 1997/49

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
93923714.5 / 0 656 887

(73) Proprietors:
- **G.D. SEARLE & CO.**
  Chicago, IL 60680-5110 (US)
- **THE MONSANTO COMPANY**
  St. Louis, MO 63166 (US)

(72) Inventors:
- **Vazquez, Michael L.**
  Gurnee, Illinois 60031 (US)
- **Mueller, Richard A.**
  Glencoe, Illinois 60022 (US)
- **Talley, John J.**
  Brentwood, MO 63144 (US)
- **Getman, Daniel**
  Chesterfield, Missouri 63017 (US)
- **Decrescenzo, Gary A.**
  St. Peters, Missouri 63376 (US)
- **Freskos, John N.**
  Clayton, Missouri 63105 (US)

(74) Representative: **Beil, Hans Christoph, Dr. et al**
Hansmann & Vogeser,
Patent- und Rechtsanwälte,
Postfach 80 01 40
65901 Frankfurt (DE)

(56) References cited:
EP-A- 0 264 795
EP-A- 0 468 641
WO-A-92/08699

EP 0 810 209 B1

Description

[0001] This application is a divisional application of the EP number 0 656 887.

BACKGROUND OF THE INVENTION

1. Filed of the Invention

[0002] The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and the use of such compounds for preparing a medicament for inhibiting retroviral proteases. This invention, in particular, relates to sulfonamide-containing hydroxyethylamine protease inhibitor compounds, a composition and the use thereof for preparing a medicament for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection.
The subject invention also relates to processes for making such compounds.

2. Related Art

[0003] During che replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virons. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral proteases.

[0004] Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

[0005] Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

[0006] Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

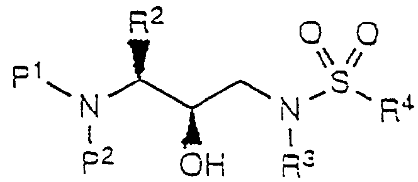
[0007] The EP-A 0 468 641 discloses 2S-hydroxy-substituted dipeptide carbonyl as well as sulfonamide derivatives which are useful as renin inhibitors.

BRIEF DESCRIPTION OF THE INVENTION

[0008] The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to the use of such compounds for preparing medicaments for inhibiting proteases, especially for inhibiting HIV protease and for treating a retroviral infection such as HIV infection and for treating AIDS, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterizued as sulfonamide-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The present invention provides retroviral protease inhibitor compounds represented by the Formula I:



(I)

wherein:

P^1 and P^2 independently represent hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R3 except for hydrogen;

wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically-acceptable salt, ester or pro-drug thereof.

[0010] Preferred compounds thereof are those wherein P^1 and P^2 independently represent hydrogen, alkoxycarbonyl, aralkyloxycarbonyl, heteroaralkoxycarbonyl, aroyl, heteroaroyl, alkanoyl, cycloalkanoyl, 3-pyridylmethyloxycarbonyl, 3-pyridylmethyloxycarbonyl N-oxide, 4-pyridylmethyloxycarbonyl, 4-pyridylmethyloxycarbonyl N-oxide, 5-pyrimidylmethyloxycarbonyl, tert-butyloxycarbonyl, allyloxycarbonyl, 2-propyloxycarbonyl, benzyloxycarbonyl, cycloheptylcarbonyl, cyclohexylcarbonyl, cyclopentylcarbonyl, benzoyl, 2-substituted benzoyl, 4-pyridylcarbonyl, 2-methylbenzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-chlorobenzoyl, 2-ethylbenzoyl, 2,6-dimethylbenzoyl, 2,3-dimethylbenzoyl, 2,4-dimethylbenzoyl, or 2,5-dimethylbenzoyl;

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl, or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl, or n-propyl; and

R^4 represents aryl, alkyl and heteroaryl, aryl, para-substituted aryl, heteroaryl, phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, or 4-pyridyl N-oxide.

[0011] Further preferred compounds are those of formula I, wherein

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl, or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl, or n-propyl; and

R^4 represents aryl, alkyl, aryl, para-substituted aryl, heteroaryl, phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl-N-oxide, 4-pyridyl or 4-pyridyl-N-oxide.

[0012] Preferred compounds are the following ones:

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-fluorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-chlorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-acetamidophenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-aminophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-fluorophenylsulfonyl) amino]-1S-(phenylmethyl) propyl] carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-chlorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-methoxyphenylsulfonyl) amino]-1S-(4-fluorophenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-fluorophenylsulfonyl) amino]-1S-(4-fluorophenylmethyl)propyl] carbamate;

Phenylmethyl[2R-hydroxy-3-[(butyl) (phenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(cyclohexylmethyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(cyclohexyl) (phenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(propyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Pentanamide, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(3-methylpropyl) (4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]-3S-methyl;

Pentanamide, 2S-[[(methylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

Pentanamide, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine;

2R-hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl) (3-methylbutyl)amino]-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl) (2-methylpropyl) amino] -1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl) (cyclohexylmethyl)amino]-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl)(cyclohexyl)amino]-1S-(phenylmethyl)propylamine;

4-Pyridinecarboxamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl];

Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl;

Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl;

Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-ethyl;

Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-chloro;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide;

Carbamic acid, [2R-hydroxy-3-[[phenylsulfonyl](2-methylpropyl)amino-]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester, N-oxide;

Carbamic acid, [2R-hydroxy-3-[[(4-chlorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

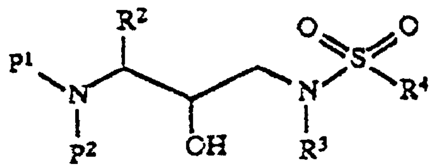
Carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-py-

ridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester; or

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester.

[0013] Other compounds according to the present invention are those represented by the formula:



(II)

wherein

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkanoyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or hetercaroyl radicals;
P^2 represents hydrogen;
R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with alkyl, halogen, $-NO_2$, -CN, CF_3, $-OR^9$ or SR^9 radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, aryl, aralkyl or heteroaralkyl radicals; and
R^4 represents alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, aryl or aralkyl radicals; and

wherein alkyl, alone or in combination, is a straight-chain or branched-chain hydrocarbon radical having from 1 to 8 carbon atoms; alkenyl, alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and from 2 to 8 carbon atoms; alkynyl, alone or in combination, means a straight -chain hydrocarbon radical having one or more triple bonds and from 2 to 10 carbon atoms; cycloalkyl, alone or in combination, is a hydrocarbon ring containing from 3 to 8 carbon atoms; aryl, alone or in combination, means a phenyl or naphthyl radical optionally substituted with alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano or haloalkyl radicals; heterocyclyl or heterocycloalkyl means a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having one or more nitrogen, oxygen or sulphur heteroatoms, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy or oxo radicals, or on a secondary nitrogen atom by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl radicals, or on a tertiary nitrogen atom by oxido radical; and heteroaryl means an aromatic heterocyclyl radical which is optionally substituted as defined above with respect to the definition of heterocyclyl;
wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically acceptable salt, ester, prodrug thereof.

[0014] Among these compounds are preferred wherein P^1 represents alkoxycarbonyl, aralkyloxycarbonyl, heteroaralkoxycarbonyl, aroyl, heteroaroyl, alkanoyl or cycloalkanoyl radicals;

R^2 represents alkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with halogen, $-OR^9$ or $-SR^9$ radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, cycloalkyl or cycloalkylalkyl radicals; and
R^4 represents alkyl, aryl or heteroaryl radicals.

[0015] Further preferred are compounds wherein P^1 represents - 3-pyridylmethyloxycarbonyl, 3-pyridylmethyloxycarbonyl N-oxide, 4-pyridylmethyloxycarbonyl, 4-pyridylmethyloxycarbonyl N-oxide, 5-pyrimidylmethyloxycarbonyl,

tert-butyloxycarbonyl, allyloxycarbonyl, 2-propyloxycarbonyl, benzyloxycarbonyl, cycloheptylcarbonyl, cyclohexylcarbonyl, cyclopentylcarbonyl, benzoyl, 2-substituted benzoyl, 4-pyridylcarbonyl, 2-methylbenzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-chlorobenzoyl, 2-ethylbenzoyl, 2,6-dimethylbenzoyl, 2,3-dimethylbenzoyl, 2,4-dimethylbenzoyl or 2,5-dimethylbenzoyl radicals;

R^2 represents benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, paramethoxybenzyl, isobutyl or n-butyl radicals;
R^3 represnts isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl or n-propyl radicals; and R^4 represents phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl or 4-pyridyl N-oxide radicals.

[0016] Also preferred are compounds of the above formula II wherein P^1 represents heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or heteroaroyl radicals;

R^2 represents alkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with halogen, $-OR^9$ or $-SR^9$ radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, cycloalkyl or cycloalkylalkyl radicals; and
R^4 represents alkyl, aryl or heteroaryl radicals; and

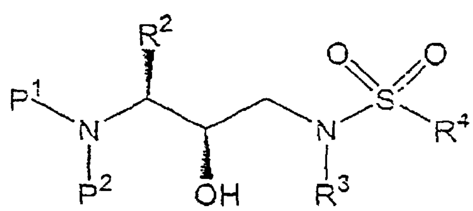
wherein heterocyclyl or heterocycloalkyl means a 5-6 ring membered heterocycle or a benzfused 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms; and heteroaryl means an aromatic 5-6 ring membered heterocycle or an aromatic benzfused 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms.

[0017] Also preferred are those compounds wherein

P^1 represents heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or heteroaroyl radicals;
R^2 represents benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, paramethoxybenzyl, isobutyl or n-butyl radicals;
R^3 represents isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl or n-propyl radicals; and

wherein heterocyclyl or heterocycloalkyl means a 5-6 ring membered heterocyle having one or two nitrogen, oxygen or sulphur heteroatoms; and heteroaryl means an aromatic 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms.

[0018] Another group of compounds according to the invention comprises a retroviral protease inhibiting compound according to claim 1 having the formula



(I)

wherein:

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalky or heteroaryl radical;

P^2 represents hydrogen;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, -C≡N. CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3 except for hydrogen;

wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycrbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically acceptable salt, prodrug, or ester thereof.

[0019] Among these are those preferred wherein

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl, or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobmyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl, or n-propyl; and

R^4 represents aryl, alkyl, aryl, para-substituted aryl, heteroaryl, phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, or 4-pyridyl N-oxide.

[0020] From the compounds of the present invention pharmaceutical compsitions comprising a pharmaceutically acceptable carrier can be prepared which are useful for preparing a medicament for treating a retroviral, especially a HIV protease or HIV-infection, especially AIDS.

[0021] As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to 10, preferably from 1 to 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, or octyl. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radial having one or more double bonds and containing from 2 to 18 carbon atoms preferably from 2 to 8 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, alkyl, or 1,4-butadienyl. The term "alkynyl", alone or in combination, means a straight-chain hydrocarbon radical having one or more triple bonds and containing from 2 to 10 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl) or butynyl. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, or tert-butoxy. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from 3 to 8, preferably from 3 to 6, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0022] The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, or 2-naphthyl.
The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, or 2-phenylethyl. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-aralkyl in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the

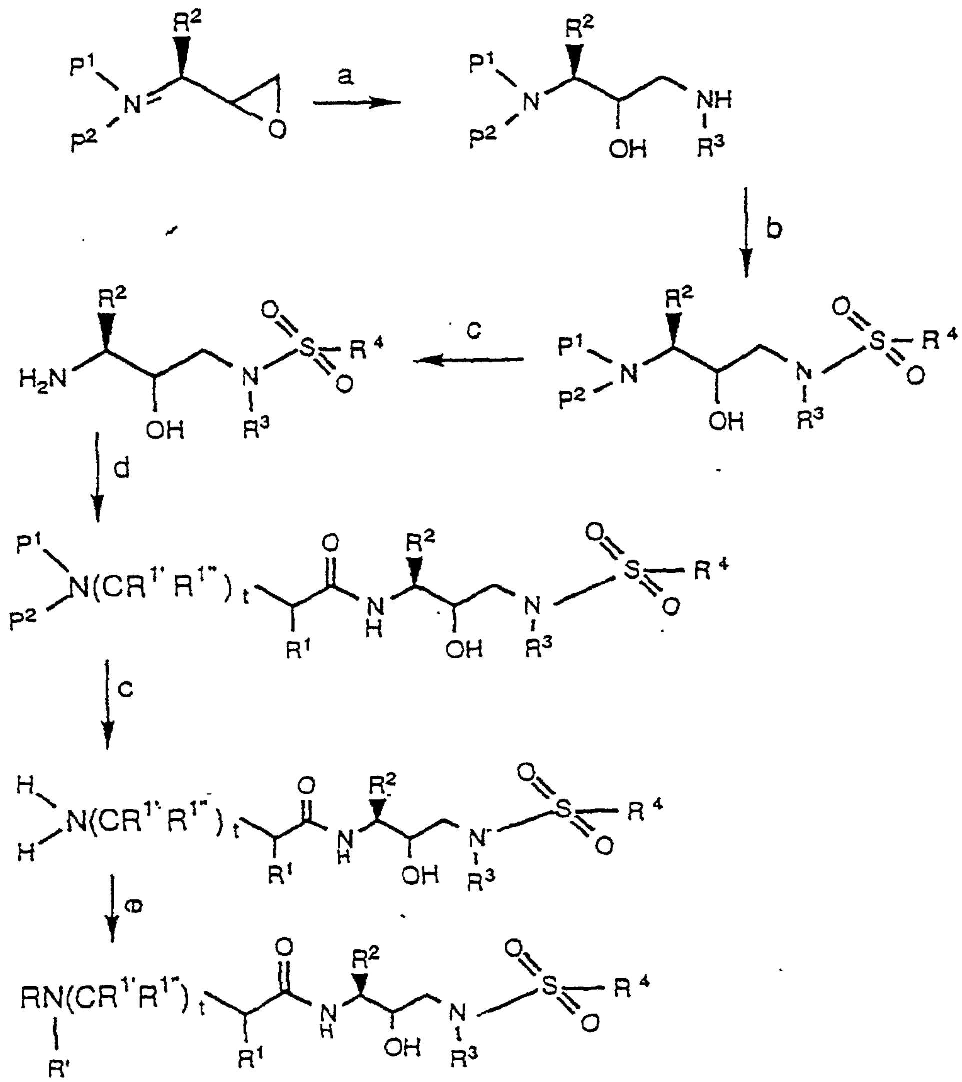
formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, or 4-methylvaleryl . The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl,or adamantanecarbonyl, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl,2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, or 4-methoxyhydrocinnamoyl.

[0023] The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, or 3-(benzyloxyformamido)-2-naphthoyl. The heterocyclyl or heterocycloalkyl portion of a heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, or heterocyclyalkyl group is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, or oxo, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tatrahydro-2-quinolyl, etc.), 1,2;3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, β-carbolinyl, 2-benzofurancarbonyl, 1-, 2-,4- or 5-benzimidazolyl. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclyloxycarbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-0-COOH wherein heteroaryl has the significance given above. The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, or cycloalkylalkyl radicals. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl or radicals . The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, or 1,1,1-trifluoroethyl. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, or toxylates.

[0024] Preferred leaving groups are indicated herein where appropriate.

[0025] Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

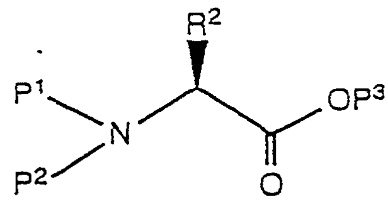
SCHEME I



a) amine b) sulfonyl chloride R^4SO_2Cl (or anhydride) + acid scavenger c) deprotection d) coupling e) coupling.

[0026] As can be seen the present compounds can be used to prepare the N-substituted amino-sulfonamides of the parent case (see reaction steps c), d) and e)).

[0027] The protected amino epoxide as shown in Scheme I can be prepared, such as in co-owned and co-pending PCT-Patent Application Serial No. PCT/US93/04804 which is incorporated herein by reference, starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



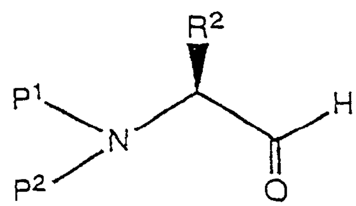
wherein P^3 represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; R^2 is as defined above; and P^1 and P^2 independently are selected from amine protecting groups, including but not limited to, arylalkyl, substituted arylalkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples of arylalkyl include, but are not limited to benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl of C_1-C_8, alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals containing cycloalkyls of C_6-C_{10}. Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, tri-fluoroacetyl, trichloroacetyl or phthaloyl.

[0028] Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

[0029] Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium flouride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-buty-dimethylsilyl chloride, phenyldimethylsilyl chlorie, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

[0030] Preferably P^1 and P^2 are independently selected from aralkyl and substituted aralkyl. More preferably, each of P^1 and P^2 is benzyl.

[0031] The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride, sodium borohydride, borane, lithium tri-ter-butoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P^1, P^2 and R^2 are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

[0032] Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chlo-

ride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydrothiaphene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutylchloroformate and DMSO. The-oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

[0033] The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

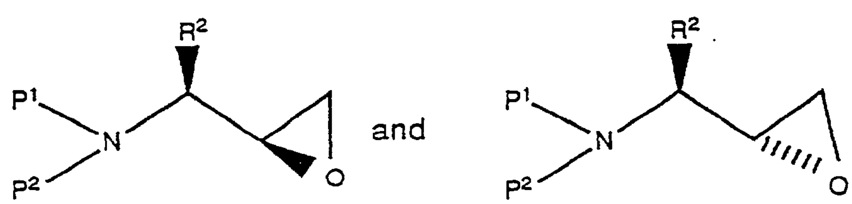
[0034] The reaction may be carried out under and inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tecramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide, acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde. precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding N-monosubstituted [either P^1 or P^2 = H] or N,N-disubstituted aldehyde.

[0035] In addition, hydride reduction of an amide or ester derivative of the corresponding alkyl, benzyl or cycloalkenyl nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenyalanine derivative can be carried out to provide the aldehydes. Hydride transfer is an additional method of aldehyde synthesis under conditions where aldehyde condensations are avoided, cf, Oppenauer Oxidation.

[0036] The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from abut 5°C to about 25°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

[0037] Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

[0038] The aldehyde resulting from the Swern oxidation is then reacted with a halomethyllithium reagent, which reagent is generated in situ by reacting an alkyllithium or arylithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry, a D-amino acid can be utilized in place of the L-amino acid.

[0039] The addition of chloromethylithium or bromomethylithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethyllithium or bromomethylithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium. Acceptable methyleneating halomethanes include chloroiodomethane, bromochloromethane, dibromomethane, diiodomethane, or bromofluoromethane. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure

solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The reaction can be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometalic reagents reagents such as methyllithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, or phenyl. The reaction can be carried out at temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple additions are preferred in certain conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

[0040] Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precurser species followed by their treatment with base to form the analogous anion. Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

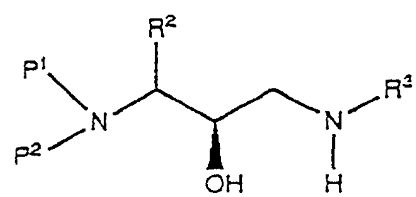
[0041] The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, methyl tosylate, methyl mesylate, methyl triflate ethyl bromide, isopropyl bromide, or or benzyl chloride in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, to provide a sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

[0042] The desired epoxides formed, using most preferred conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivilants of camphor sulfonic acid, citric acid, camphoric acid, or 2-methoxyphenylacetic acid can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled in the art.

[0043] The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula:

$$R^3NH_2$$

wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e. g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, or isopropanol, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. Exemplary . amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, or naphthylene methyl amine The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formula

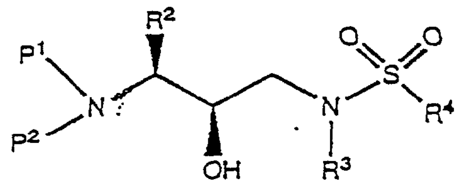


wherein P^1, P^2, R^2 and R^3 are as described above.
Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

[0044] The amino alcohol defined above is then reacted in a suitable solvent with a sulfonyl chloride (R^4SO_2Cl) or

sulfonyl anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. Preferred sulfonyl chlorides are methanesulfonyl chloride and benzenesulfonyl chloride. The resulting sulfonamide derivative can be represented,

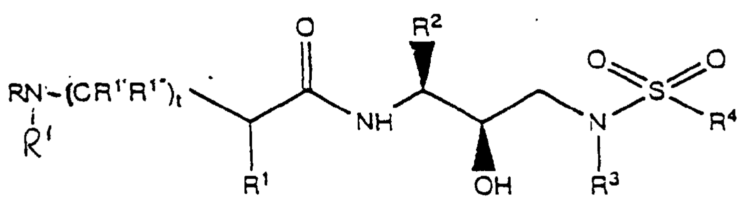
by the formula



wherein P^1, P^2, R^2, R^3 and R^4 are as defined above. These intermediates are useful for preparing inhibitor compounds of the parent case and are also active inhibitors of retroviral proteases.

[0045] The sulfonyl halides of the formula R^4SO_2X can be prepared by the reaction of a suitable Grignard or alkyl lithium reagent with sulfuryl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic acids may be converted to sulfonyl halides using reagents such as PCl_5, and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Such sulfonic acids are also commercially available. In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the $-SO_2-$ moiety is replaced by an -SO- or -S- moiety, respectively.

[0046] The following preparation of the sulfonamide derivative of the parent case, the amino protecting group P^1 and P^2 are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis or hydrogenolysis to produce the antiviral compounds of the parent case having the formula:



[0047] Contemplated equivalents of the general formulas set torch above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, or amino functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

[0048] The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the arc, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

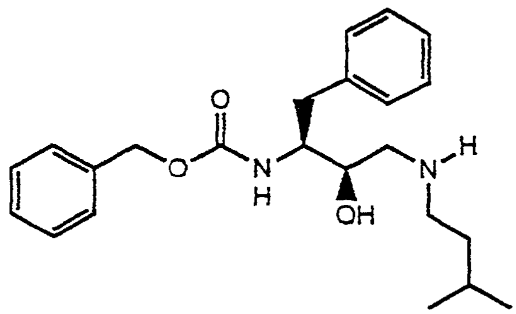
[0049] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative.

[0050] All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

[0051] The following Examples 1 through 7 illustrate preparation of the present compounds. These are useful in preparing the inhibitor compounds of the parent case.

Example 1A

[0052]



Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

Part A:

[0053] To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+$ = 340.

Part B:

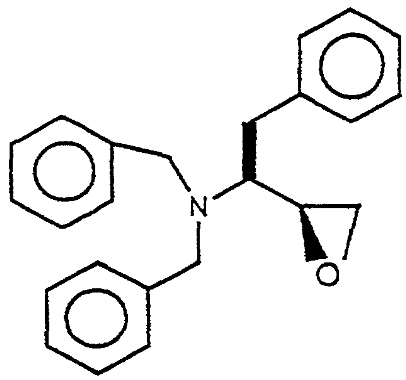
[0054] To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH^+ 298.

Part C:

[0055] A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated *in vacuo* and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The product was isolated-by filtration and air dried to give 1.18g, 95% of N=[[3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C, MH^+ m/z = 371.

Example 1B

[0056]



Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

Step A:

[0057] A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) was heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) was then slowly added (addition time ~25 min). The mixture was then stirred at 97°C for 30 minutes. The solution was cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers were then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product was then used in the next step without purification.

Step B:

[0058] The crude benzylated product of the above step was dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) was then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The mixture was stirred for 20 minutes at -55°C. The reaction was quenched at -55°C by the slow addition of methanol (37 ml). The cold solution was then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture was cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid was dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) were then added to the residue upon which the alcohol product began to crystallize. After 30 min., an additional 50 ml hexane was added to promote further crystallization. The solid was filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material could be isolated by refiltering the mother'liquor. The solids were combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors were combined and concentrated (34 g). The residue was treated with ethyl acetate and hexane which provided an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

[0059] Alternatively, the alcohol was prepared from L-phenylalaninol. L-phenylalaninol (176.6 g, 1.168 mol) was added to a stirred solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65°C under a nitrogen atmosphere. A solution of benzyl bromide (400 g, 2.339 mol) in 3A ethanol (305 mL) was added at a rate that maintained the temperature between 60-68°C. The biphasic solution was stirred at 65°C for 55 min and then allowed to cool to 10°C with vigorous stirring. The oily product solidified into small granules. The product was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. The crude product obtained was air dried overnite to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at -8°C), washed with 1.6 L of cold (-10°C) ethyl acetate/heptane (1: 10 by volume) and air-dried to give 339 g (88% yield) of βS-2-[Bis(phenylmethyl)amino]benzene-propanol, mp

71,5-73.0°C. More product can be obtained from the mother liquor if necessary. The other analytical characterization was identical to compound prepared as described above.

Step C:

[0060] A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C. A solution 'of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was concentrated to give the desired aldehyde product. The aldehyde was carried on to the next step without purification.

[0061] Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.

[0062] Alternatively, the. aldehyde was prepared as follows. (200 g, 0.604 mol) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to 12°C and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to maintain the temperature between 8-17°C (addition time - 1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled with ice water and quenced with 1.6 L of cold water (10-15°C) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), and brine (2.2 L), dried over $MgSO_4$ (280 g) and filtered. The solvent was removed on a rotary evaporator at 35-40°C and then dried under vaccuum to give 198.8 g of αS-[Bis-(phenylmethyl)amino]-benzenepropanaldehyde as a pale yellow oil (99.9%). The crude product obtained was pure enough to be used directly in the next step without purification. The analytical data of the compound were consistent with the published literature. $[\alpha]_D25$ = -92.9 ° (c 1.87, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) ∂, 2.94 and 3.15 (ABX-System, 2H, J_{AB}= 13.9 Hz, J_{AX}= 7.3 Hz and J_{BX} = 6.2 Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, J_{AB}= 13.7 Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS calcd for (M+1) $C_{23}H_{24}NO$ 330.450, found: 330.1836. Anal. Calcd. for $C_{23}H_{23}ON$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase:(S,S) Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enanatiomer 10.62 min.

Step D:

[0063] A solution of αS-[Bis(phenylmethyl)amino] benzene-propanaldehyde (191.7 g, 0.58 mol) and chloroiodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloroiodomethane (17 mL) was added, followed by n-butyllithium (110 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (55 mL, 0.088 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloroiodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyllithium (37 mL, 0.059 mol) at <-25°C. After addition, the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), Rf = 0.29 &

0.32, respectively. An analytical sample of each of the diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:

N,N,αS-Tris(phenylmethyl)-2S-oxiranemethanamine

^{1}H NMR (400 MHz, $CDCl_3$) ∂ 2.49 and 2.51 (AB-System, 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} = 10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB} = 14.00), 7.21 (m, 15H); ^{13}C NMR (400 MHz,$CDCl_3$) ∂ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS calcd for $C_{24}H_{26}NO$ (M+1) 344.477, found 344.2003.

N,N,αS-Tris(phenylmethyl)-2R-oxiranemethanamine

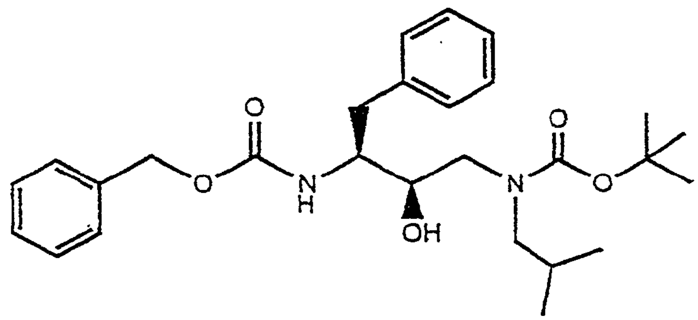
^{1}H NMR (300 MHz, $CDCl_3$) ∂ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H).HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of (8): 9.38 min., retention time of enanatiomer of (4): 13.75 min.

[0064] Alternatively, a solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyllithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

[0065] Alternatively, a solution of αS-[Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional bromochloromethane (14 mL) was added, followed by n-butyllithium (102 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyllithium (51 mL, 0.082 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

Example 2

[0066]

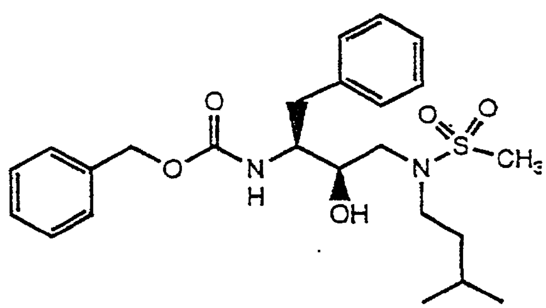


Preparation of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane

[0067] To a solution of 7.51g (20.3 mmol) of N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenylbutyl] -N-(2-methylpropyl)]amine in 67 mL of anhydrous tetrahydrofuran was added 2.25g (22.3 mmol) of triethylamine. After cooling to 0°C, 4.4g (20.3 mmol) of di-tert-butyldicarbonate was added and stirring continued at room temperature for 21 hours. The volatiles were removed in vacuo, ethyl acetate added, then washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 9.6g of crude product. Chromatography on silica gel using 30% ethyl acetate/hexane afforded 8.2g of pure N-[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane, mass spectum m/e = 477 (M+Li).

Example 3A

[0068]

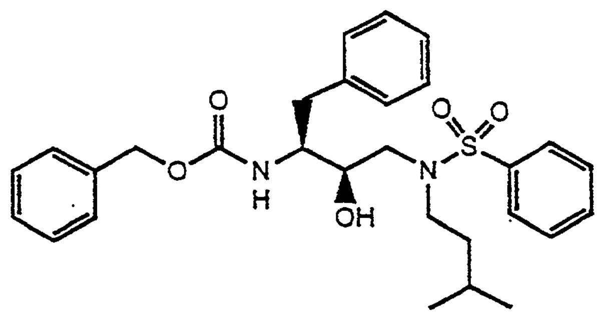


Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

[0069] To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (2.0 gm, 5.2 mmol) and triethylamine (723 uL, 5.5 mmol) in dichloromethane (20 mL) was added dropwise methanesulfonyl chloride. (400 uL, 5.2 mmol). The reaction mixture was stirred for 2 hours at room temperature, then the dichloromethane solution was concentrated to ca. 5 mL and applied to a silica gel column (100 gm). The column was eluted with chloroform containing 1% ethanol and 1% methanol. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (methylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd for $C_{24}H_{34}N_2O_5S$: C, 62.31; H, 7.41; N, 6.06. Found: C, 62.17; H, 7.55; N, 5.97.

Example 3B

[0070]

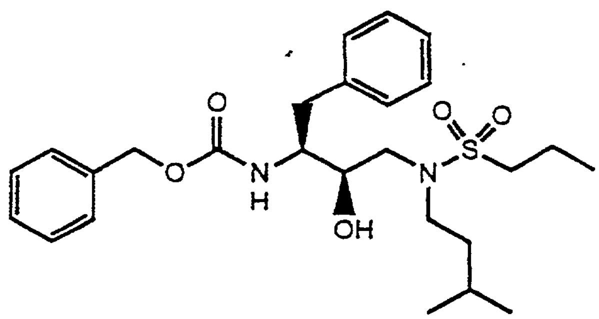


Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

[0071] From the reaction of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzenesulfonyl chloride (483 uL, 3.8 mmol) one obtains phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-carbamate. -Column chromotography on silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

Example 4

[0072]

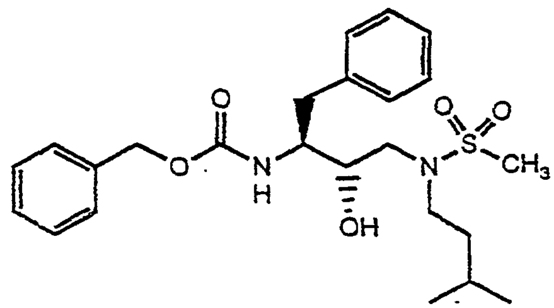


Preparation of Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate

[0073] To a solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg , 0.5 mmol) and triethylamine (139 uL, 1.0 mmol) in dichloromethane (10 mL) was added dropwise trimethylsilyl chloride (63 uL, 0.5 mmol). The reaction was allowed to stir for 1 hour at room temperature, cooled to 0° C with an ice bath and then n-propanesulfonyl chloride (56 uL, 0.5 mmol) was added dropwise. The reaction mixture was stirred for 1.5 hours at room temperature, then diluted with ethyl acetate (50 mL) and washed sequentially with IN HCl, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution (25 mL each). The organic solution was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was stirred with methanol (10 mL) for 16 hours, concentrated and the residue chromatographed on silica gel (50 gm) eluting with 10% ethyl acetate in hexane (450 mL), then with 1:1 ethyl acetate / hexane. The phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (n-propanesulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was recrystallized from ethyl ether / hexane to afford a white solid Anal. Calcd. for $C_{26}H_{38}N_2O_5S$: C, 63.64; H, 7.81; N, 5.71. Found: C, 63.09; H, 7.74; N, 5.64.

Example 5

[0074]



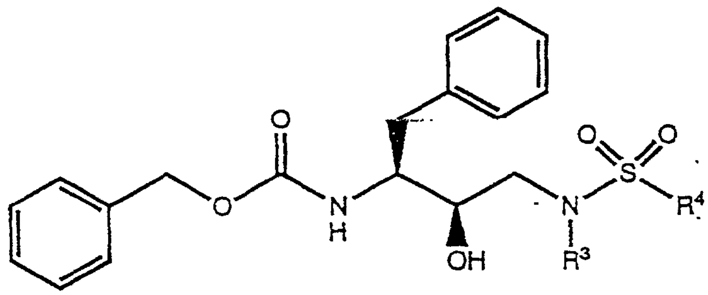
[0075] The procedure described in Example 2 was used to prepare phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate.

[0076] To a solution of N[3(S)-benzyloxycarbonylamino-2(S)-hydroxy-4-phenylbutyl] N-isoamylamine (192 mg, 0.5 mmol) and triethylamine (139 uL, 0.55 mmol) in dichloromethane (8 mL) was added dropwise methanesulfonyl chloride (39 uL, 0.55 mmol). The reaction mixture was stirred for 16 hours at room temperature, then the dichloromethane solution was applied to a silica gel column (50 gm). The column was eluted with dichloromethane containing 2.5% methanol. The phenylmethyl [2S-hydroxy-3-[(3-methylbutyl) (methylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate was obtained as a white solid Anal. Calcd. for $C_{24}H_{34}N_2O_5S$ ◊ 0.2 H_2O: C, 61.83; H, 7.44; N, 6.01. Found: C, 61.62; H, 7.40; N, 5.99.

Example 6

[0077] Following the procedures of the previous Examples 1-5, the intermediate compounds set forth in Tables 1A and 1B were prepared.

TABLE 1A



Entry	R^3	R^4
1	isoamyl	p-fluorophenyl
2	isoamyl	p-nitrophenyl
3	isoamyl	o-nitrophenyl
4	isoamyl	ß-naphthyl
5	isoamyl	2-thienyl
6	isoamyl	benzyl
7	isobutyl	p-fluorophenyl
8	p-fluorobenzyl	phenyl
9	4-pyridylmethyl	phenyl
10	cyclohexylmethyl	phenyl
11	allyl	phenyl
12	propyl	phenyl
13	cyclopropylmethyl	phenyl
14	methyl	phenyl
15	propargyl	phenyl
16	isoamyl	p-chlorophenyl

TABLE 1A (Cont'd)

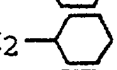
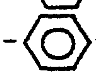
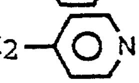
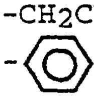
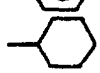
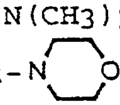
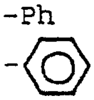
Entry	R^3	R^4
17	isoamyl	p-methoxyphenyl
18	isoamyl	m-nitrophenyl
19	isoamyl	m-trifluoromethylphenyl
20	isoamyl	o-methoxycarbonylphenyl
21	isoamyl	p-acetamidophenyl
22	isobutyl	phenyl
23	$-CH_2Ph$	-Ph
24	$-CH_2-$  -F	-Ph
25	$-CH_2$ 	-Ph
26	$-CH_2-$  $-OCH_3$	-Ph
27	$-CH_2$ 	-Ph
28	$-CH_2$ 	-Ph
29	$-CH_2CH{=}CH_2$	-Ph
30	- 	-Ph
31		-Ph
32	$-CH_2CH_2Ph$	-Ph
33	$-CH_2CH_2CH_2CH_2OH$	-Ph
34	$-CH_2CH_2N(CH_3)_2$	-Ph
35	$-CH_2CH_2-$ 	-Ph
36	$-CH_3$	-Ph
37	$-CH_2CH_2CH_2SCH_3$	-Ph
38	$-CH_2CH_2CH_2S(O)_2CH_3$	-Ph
39	$-CH_2CH_2CH(CH_3)_2$	- 
40	$-CH_2CH_2CH(CH_3)_2$	$-CH_2CH_2CH_3$

TABLE 1A (Cont'd)

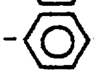
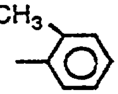
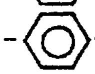
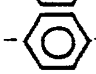
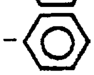
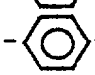
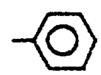
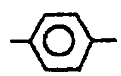
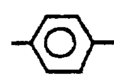
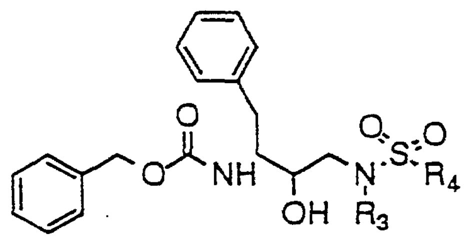
Entry	R^3	R^4
41	$-CH2CH2CH(CH3)2$	$-CH3$
42	$-CH2CH2CH(CH3)2$	-  -F
43	$-CH2CH2CH(CH3)2$	-  $-CH3$
44	$-CH2CH2CH(CH3)2$	CO_2CH_3 
45	$-CH2CH(CH3)2$	-  -F
46	$-CH2CH(CH3)2$	-  -NHAc
47	$-CH2CH(CH3)2$	-  $-CH3$
48	$-CH2CH2CH3$	-  $-OCH3$
49	$-CH2CH2CH2CH3$	-  $-OCH3$
50	$-CH_2CH_2CH(CH_3)_2$	$-CF_3$
51	$-CH_2CH(CH_3)_2$	$-CH_3$
52	$-CH_2CH_2CH(CH_3)_2$	$-CH_2Cl$
53	$-CH_2CH(CH_3)_2$	$-CH_2=CH$ 
54	$-CH_2CH(CH_3)_2$	 OCH_3
55	$-CH_2CH(CH_3)_2$	$-CH=CH_2$
56	$-CH_2-CH)CH_3)(CH_2CH_3)$	 OCH_3

TABLE 1A (Cont'd)

Entry



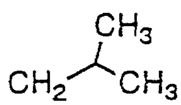
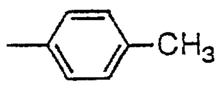
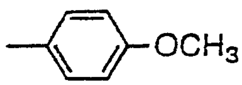
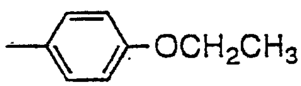
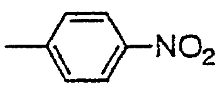
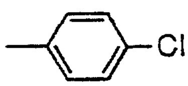
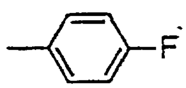
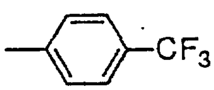
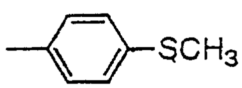
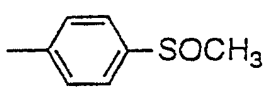
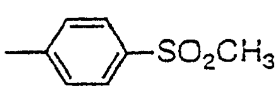
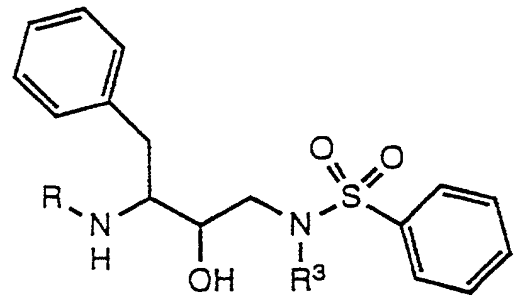
Entry	R^3	R^4	MASS MEASUREMENT MOL FORM	CALC	FOUND
1			$C_{29}H_{36}N_2O_5S$	531 (M+Li)	531
2			$C_{29}H_{36}N_2O_6S$	541(M+H)	541
3			$C_{30}H_{36}N_2O_6S$	555.2529 (M+H)	555.2582
4					
5					
6			$C_{28}H_{33}N_2O_5SF$	529.2172 (M+H)	521.2976
7					
8			$C_{29}H_{36}N_2O_5S_2$	563 (M+Li)	563
9			$C_{29}H_{36}N_2O_6S_2$	573(M+H)	573
10			$C_{29}H_{36}N_2O_7S_2$	595 (M+Li)	595

TABLE 1B



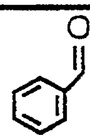
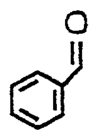
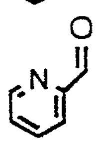
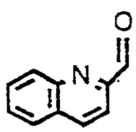
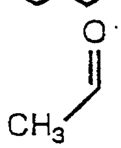
Entry	R	R^3
1		$-CH_2Ph$
2		$-CH_2CH_2CH(CH_3)_2$
3		$-CH_2CH(CH_3)_2$
4		$-CH_2CH(CH_3)_2$
5		$-CH_2CH(CH_3)_2$

TABLE 1B (Cont'd)

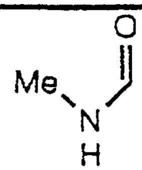
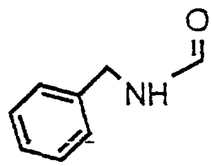
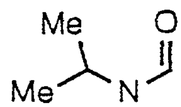
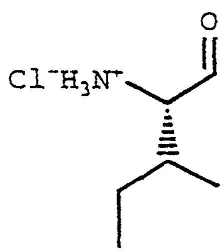
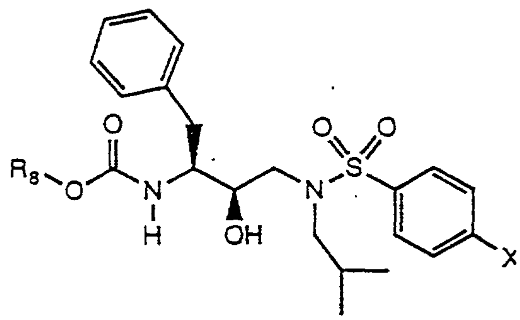
Entry	R	R^3
6		$-CH_2CH(CH_3)_2$
7		$-CH_2CH(CH_3)_2$
8		$-CH_2CH(CH_3)_2$
9		$-CH_2CH_2(CH_3)_2$

Table 1C



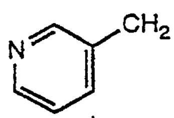
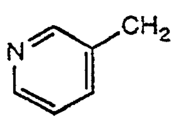
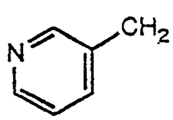
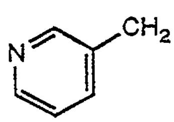
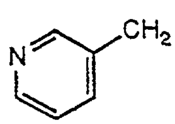
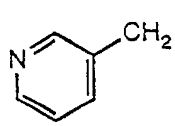
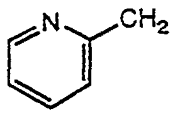
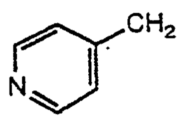
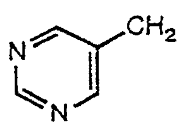
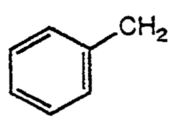
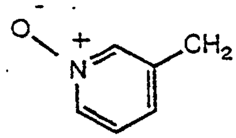
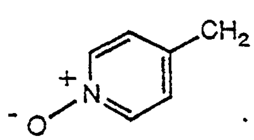
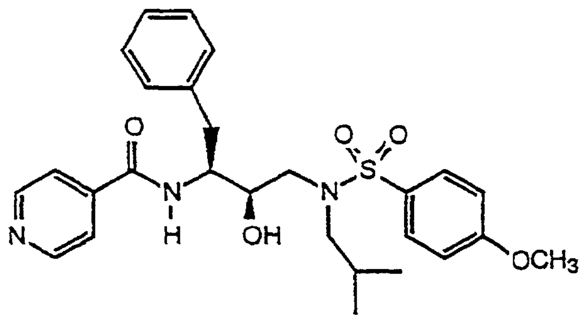
X	R^8	FORMULA	Mass Determination Calc	Found
H		$C_{27}H_{33}N_3O_5S$	512.2219(M+H)	521.2267
OCH_3		$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2434
F		$C_{27}H_{32}N_3O_5SF$	530(M+H)	530
Cl		$C_{27}H_{32}N_3O_5SCl$	546(M+H)	546
NO_2		$C_{27}H_{32}N_4O_7S$	557(M+H)	557
OH		$C_{27}H_{33}N_3O_6S$	528(M+H)	528

TABLE 1C (Cont'd)

X	R^8	FORMULA	Mass Determination Calc	Found
OCH_3		$C_{28}H_{35}N_3O_6S$	542.2325(M+H)	542.2362
OCH_3		$C_{28}H_{35}N_3O_6S$	548.2407(M+Li)	548.2393
OCH_3		$C_{28}H_{35}N_3O_6S$	543(M+H)	543
OCH_3		$C_{29}H_{36}O_6N_2S$	547.2454(M+Li)	547.2475
OCH_3	tert-Butyl	$C_{26}H_{38}N_2O_6S$	513.2611(M+Li)	513.2593
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M+Li)	564
OCH_3		$C_{28}H_{35}N_3O_7S$	564(M+Li)	564

Example 7A

[0078]

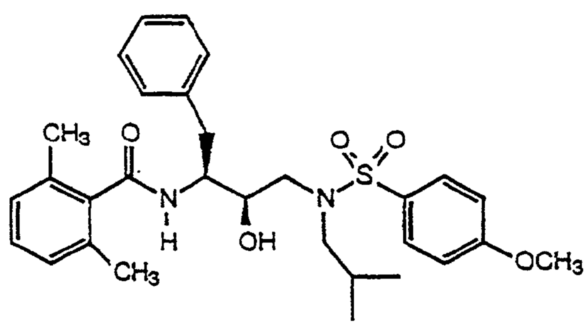


Preparation of 4-Pyridinecarboxamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]

[0079] To a solution of 231 mg (0.57 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl] amino-1S-(phenylmethyl)propylamine in 3 mL of methylene chloride at O C, was added 288 mg(2.85 mmol) of triethylamine and then 112 mg(0.63 mmol) of isonicotinoyl chloride hydrochloride. After 19 hours at room temperature, the solvent was removed, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried with magnesium sulfate, filtered and concentrated to afford 290 mg of crude product. This was chromatographed on silica gel using 3-5% isopropanol/methylene chloride as eluent to afford 190 mg of the desired compound; mass spectrum calc. for $C_{27}H_{34}N_3O_5S$ (M + H) 512.2219; found 512.2280.

Example 7B

[0080]



Preparation of Benzamide, N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl

[0081] To a solution of 83 mg (0.55 mmol) of 2,6-dimethylbenzoic acid and 125 mg (0.82 mmol) of N-hydroxybenzotriazole in 3 mL of anhydrous DMF at O C was added 117 mg (0.61mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After 2 hours at O C, 203 mg (0.50 mmol) of 2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine was added. After 22 hours at room temperature, the solvent was removed in vacuo, ethyl acetate added, then washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated to afford 300 mg of crude product. Chromatography on silica gel using 20-50% ethyl acetate/hexane afforded 37 mg of the desired product; mass spectrum calcd for $C_{30}H_{38}N_2O_5S$ (M+H) 539.2580; found 539.2632.

Example 8

[0082] The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC_{50} (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 16. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO_2)-Gln-ArgNH_2. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)] The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4
20% glycerol
1 mM EDTA
1 mM DTT
0.1% CHAPS

[0083] The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM.

[0084] HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

[0085] The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10μl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40μl of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

[0086] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

TABLE 2A

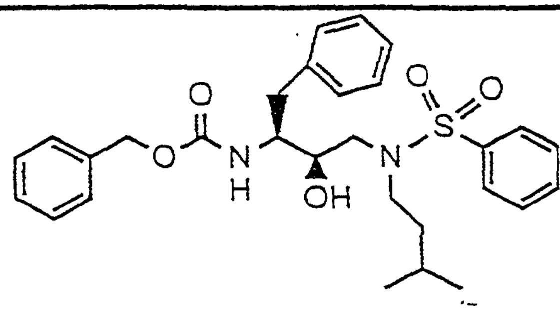
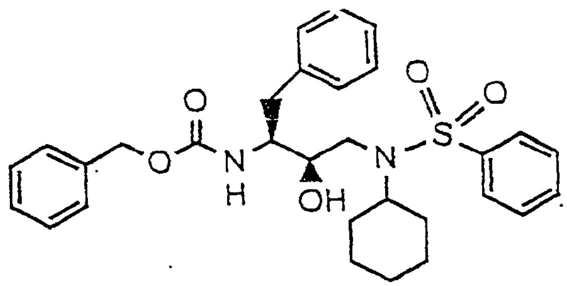
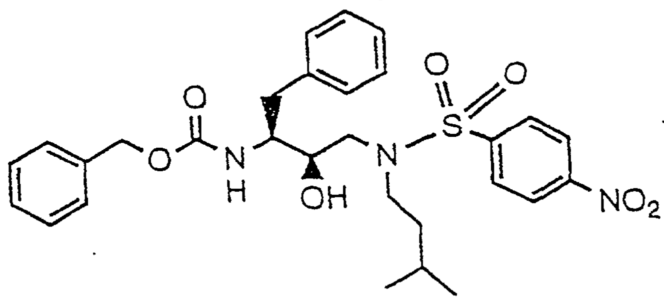
Entry	Compound	IC50 (nanomolar)
1		16
2		19
3		10

TABLE 2A (Cont'd)

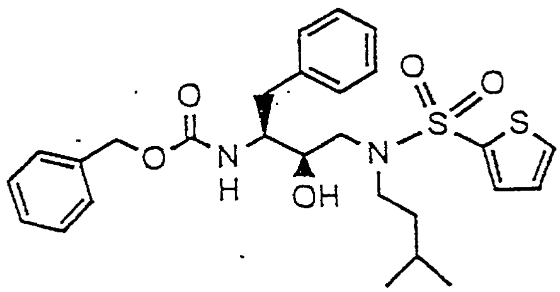
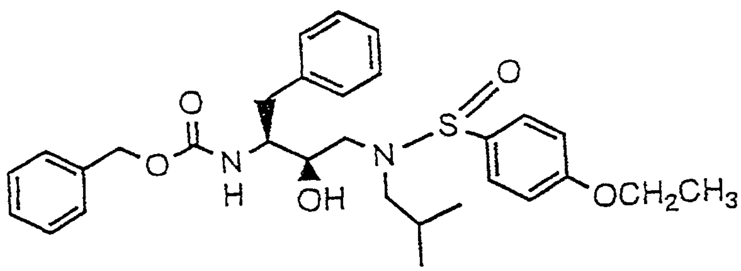
Entry	Compound	IC50 (nanomolar)
4		100
5		20

TABLE 2B

Ex.	Table	Entry	IC_{50}(uM) or % inhib
6	1a	1	0.011
6	1a	2	0.010
6	1a	3	38% @ 1 uM, 79% @ 10 uM
6	1a	4	0.016
6	1a	5	0.10
6	1a	6	36% @ 10 uM
6	1a	7	0.0096
6	1a	39	0.016
6	1a	40	0.21
6	1a	41	24% @ 1uM, 74% @ 10 uM
6	1a	50	42% @ 1uM, 89% @ 10 uM
6	1a	51	31% @ 1uM, 76% @ 10 uM
6	1a	52	39% @ 1 uM, 81% @ 10 uM
6	1a	53	0.049
6	1a	54	0.0028
6	1a	55	0.10
6	1a	56	0.0036

Example 9

[0087] The effectiveness of the compounds listed in Table 2 were determined in the above-described enzyme assay and in a CEM cell assay.

[0088] The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, J. Virol. Methods, 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a $CD4^+$ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2µg/ml). An 80 µl volume of medium containing 1 x 10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100µl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5 x 10^4 $TCID_{50}$ per ml ($TCID_{50}$ = the dose of virus that infects 50% of cells in tissue culture), and a 20µL volume of the virus sample (containing 1000 $TCID_{50}$ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture places contained the following experiments:

	Cells	Drug	Virus
1.	+	-	-
2.	+	+	-
3.	+	-	+
4.	+	+	+

[0089] In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 µg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

[0090] Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO_2 atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells- in each well were resuspended and a 100µl sample of each cell suspension was removed for assay. A 20µL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100µL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO_2 environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100µl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

TABLE 3

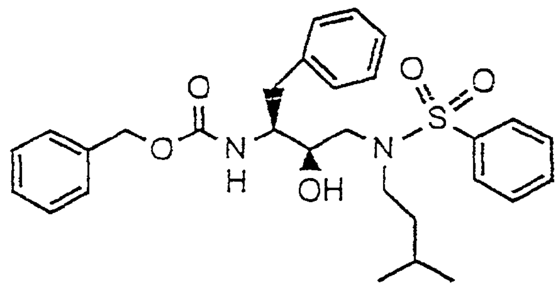
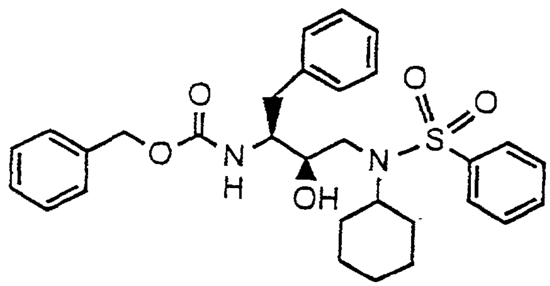
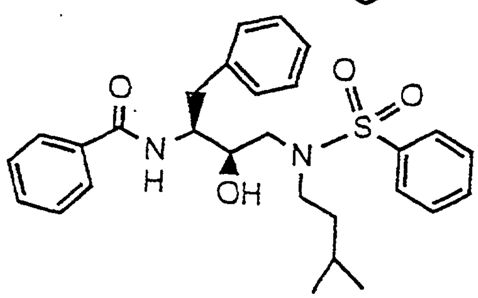
Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
1		16	55	27
2		19	88	11
3		85	1200	24

TABLE 3 (Cont'd)

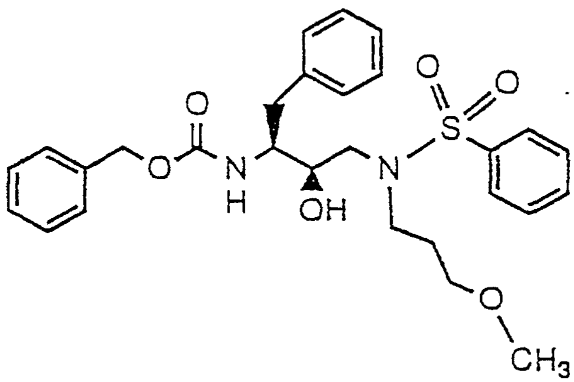
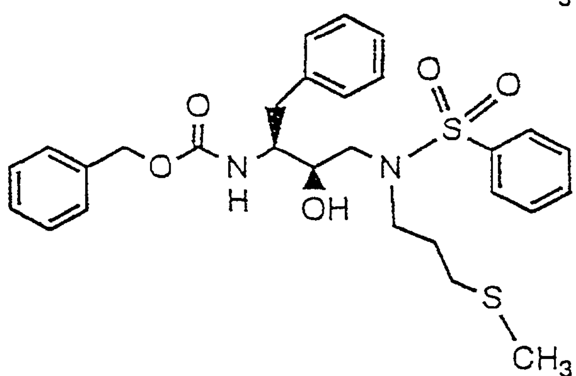
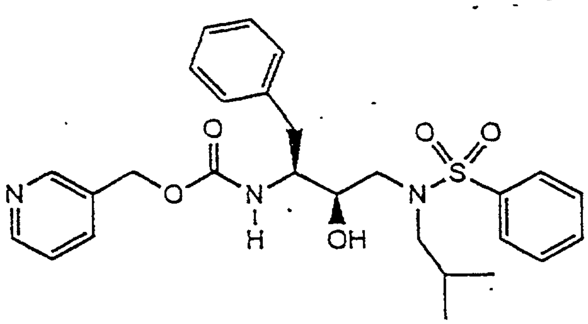
Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
4		53	398	15
5		45	700	12
6		9	80	62,000

TABLE 3. (Cont'd)

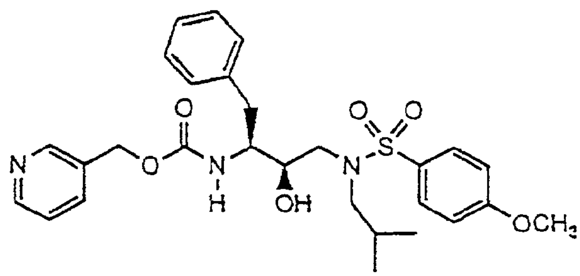
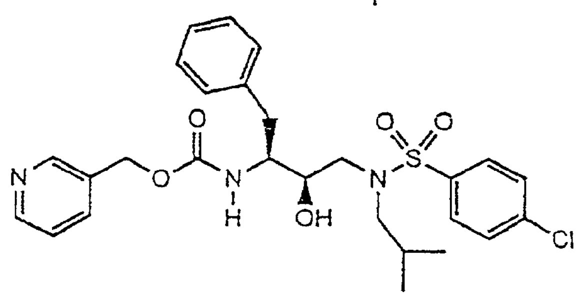
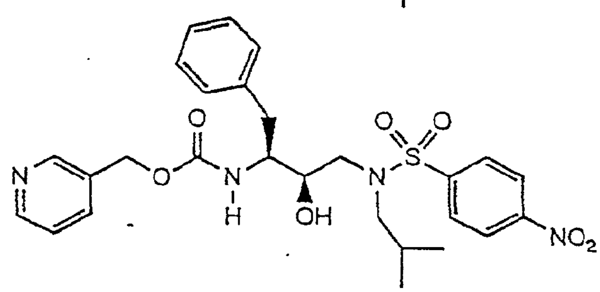
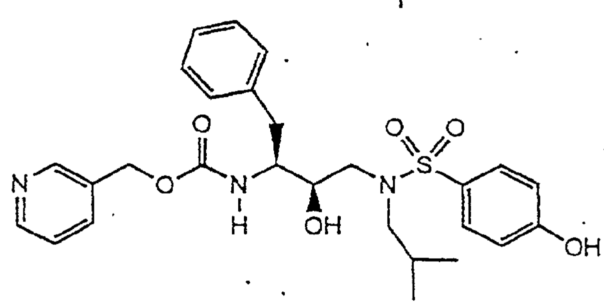
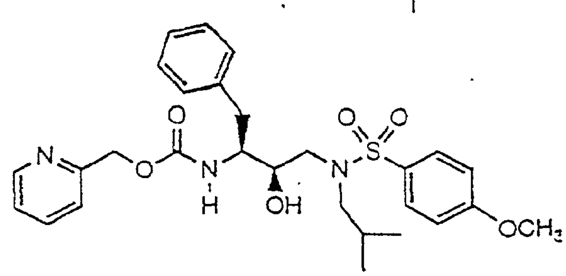
Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
7		4	5	59,000
8		4		
9		8		
10		4		
11		73		

TABLE 3 (Cont'd)

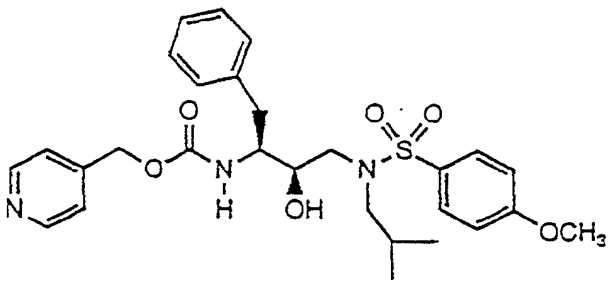
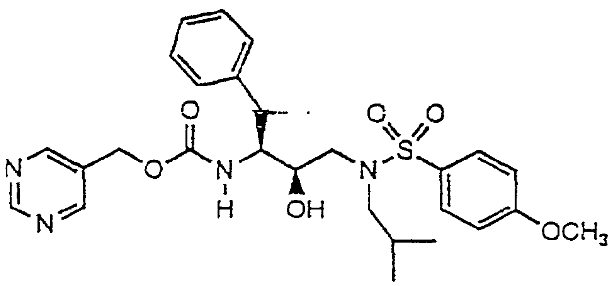
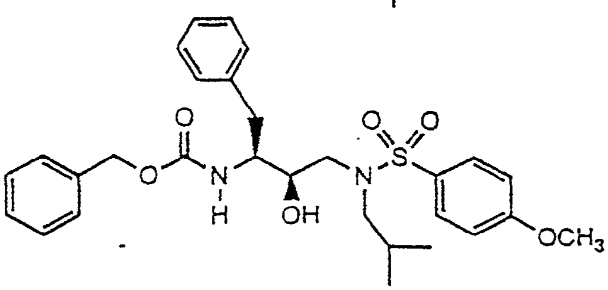
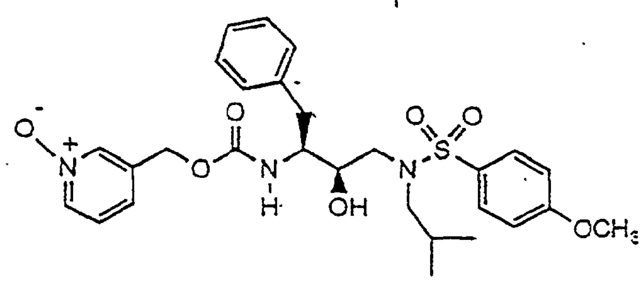
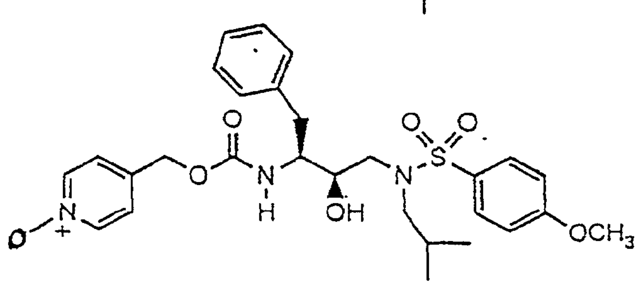
Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
12		15	18	31,000
13		2		
14		3		
15		60	120	167,000
16				

TABLE 3 (Cont'd)

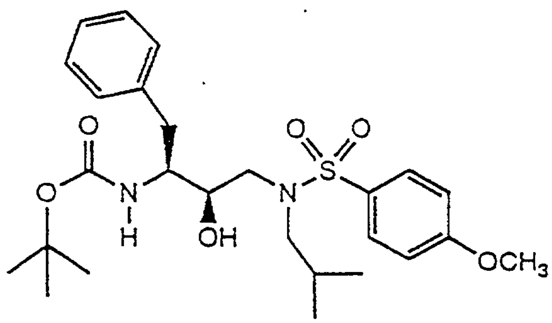
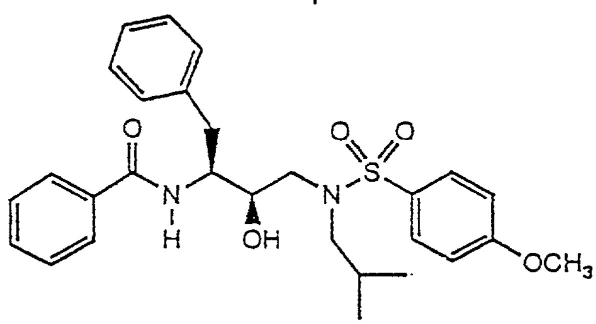
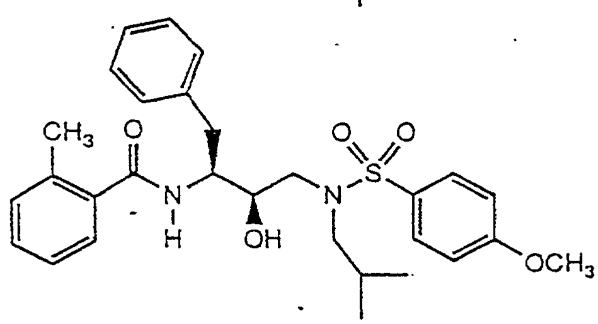
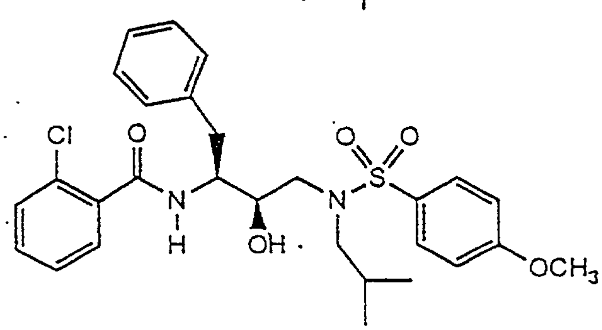
Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
17		5	177	300,000
18		14	76	213,000
19		5	105	196,000
20		6	154	154,000

TABLE 3 (Cont'd)

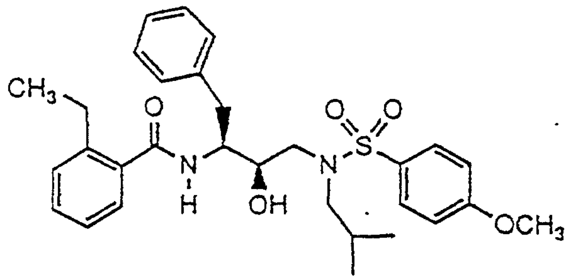
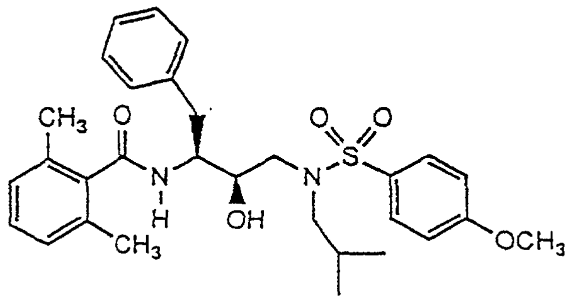
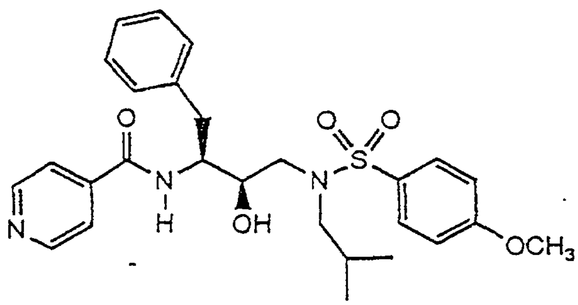
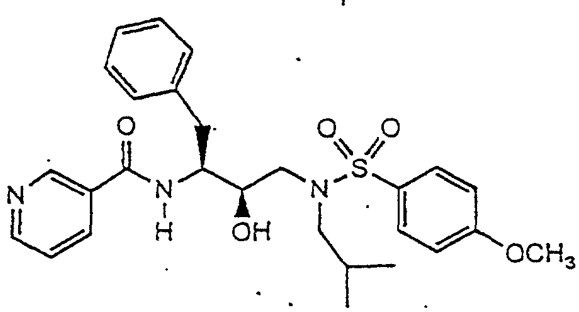
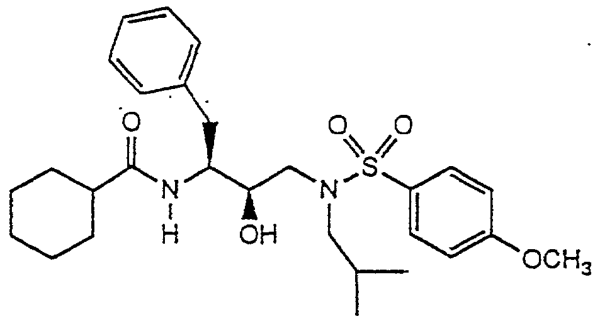
Entry	Compound	IC_{50} (nm)	EC_{50} (nm)	TD_{50} (nm)
21		10		
22		5	98	17,000
23		18	68	
24		67	188	

TABLE 3 (Cont'd)

Entry	Compound	IC50 (nm)	EC50 (nm)	TD50 (nm)
25		18		

[0091] The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simia immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or proplylaxis of retroviral infections.

[0092] Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacecyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation or the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

[0093] The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenechyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0094] Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth mecals, such as sodium, potassium, calcium or magnesium or with organic bases.

[0095] Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts

of submultiples thereof to make up the daily dose.

[0096] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host created and the particular mode of administration.

[0097] The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

[0098] The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

[0099] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0100] Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

[0101] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

[0102] Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting. agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

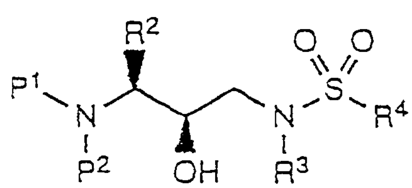
[0103] While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

[0104] The foregoing is merely illustrative of the invention.

[0105] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention.

Claims

1. A compound represented by the formula:



(I)

wherein:

P^1 and P^2 independently represent hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, amino alkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3 except for hydrogen;

wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycrbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically acceptable salt, ester, or prodrug thereof.

2. Compound of claim 1 wherein:

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl, or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl, or n-propyl; and

R^4 represents aryl, alkyl, aryl, para-substituted aryl, heteroaryl, Phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, or 4-pyridyl N-oxide.

3. Compound of Claim 1 wherein P^1 and P^2 independently represent hydrogen, alkoxycarbonyl, aralkyloxycarbonyl, heteroaralkoxycarbonyl, aroyl, heteroaroyl, alkanoyl, cycloalkanoyl, 3-pyridylmethyloxycarbonyl, 3-pyridylmethyloxycarbonyl N-oxide, 4-pyridylmethyloxycarbonyl, 4-pyridylmethyloxycarbonyl N-oxide, 5-pyrimidylmethyloxycarbonyl, tert-butyloxycarbonyl, allyloxycarbonyl, 2-propyloxycarbonyl, benzyloxycarbonyl, cycloheptylcarbonyl, cyclohexylcarbonyl, cyclopentylcarbonyl, benzoyl, 2-substituted benzoyl, 4-pyridylcarbonyl, 2-methylbenzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-chlorobenzoyl, 2-ethylbenzoyl, 2,6-dimethylbenzoyl, 2,3-dimechylbenzoyl, 2,4-dimethylbenzoyl or 2,5-dimethylbenzoyl;

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl or n-propyl; and

R^4 represents aryl, alkyl and heteroaryl, aryl, para-substituted aryl, phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl,

3-pyridyl N-oxide, 4-pyridyl or 4-pyridyl N-oxide.

4. A compound of Claim 1 which is:

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-fluorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-chlorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-acetamidophenylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-aminophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-fluorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamate;

Phenylmethyl[2R-hydroxy-3-[(3-methylbutyl) (4-chlorophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-methoxyphenylsulfonyl) amino]-1S-(4-fluorophenylmethyl) propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl) (4-fluorophenylsulfonyl) amino]-1S-(4-fluorophenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(butyl)(phenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(cyclohexylmethyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(cyclohexyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Phenylmethyl[2R-hydroxy-3-[(propyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate;

Pentanamide, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl] -3S-methyl;

Pentanamide, 2S-[[(methylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

Pentanamide, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine;

2R-hydroxy-3-[(2-methylpropyl)(4-hydroxypnenyl)sulfonyl]amino-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl)(3-methylbutyl) amino]-1S-(phenylmethyl) propylamine;

[2R-hydroxy-3-[(phenylsulfonyl)(2-methylpropyl) amino]-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl)(cyclohexylmethyl)amino]-1S-(phenylmethyl)propylamine;

[2R-hydroxy-3-[(phenylsulfonyl)(cyclohexyl)amino]-1S-(phenylmethyl)propylamine;

4-Pyridinecarboxamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl) sulfonyl](2-methylpropyl) amino] -1S-(phenylmethyl)propyl];

Benzamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl;

Benzamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl;

Benzamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-ethyl;

Benzamide,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-chloro;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester, N-oxide;

Carbamic acid, [2R-hydroxy-3-[[phenylsulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2 - methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester, N-oxide;

Carbamic acid, [2R-hydroxy-3-[[(4-chlorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

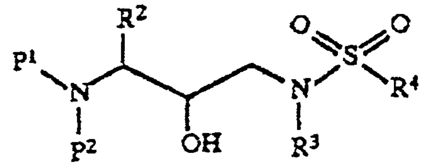
Carbamic acid, [2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-fluorophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbamic acid, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester; or

Carbamic acid, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester.

5. A compound represented by the formula:



wherein

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkanoyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or heteroaroyl radicals;
P^2 represents hydrogen;
R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with alkyl, halogen, $-NO_2$, -CN, CF_3, $-OR^9$ or SR^9 radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, aryl, aralkyl or heteroaralkyl radicals; and
R^4 represents alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, aryl or aralkyl radicals; and

wherein alkyl, alone or in combination, is a straight-chain or branched-chain hydrocarbon radical having from 1 to 8 carbon atoms; alkenyl, alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and from 2 to 8 carbon atoms; alkynyl, alone or in combination, means a straight -chain hydrocarbon radical having one or more triple bonds and from 2 to 10 carbon atoms; cycloalkyl, alone or in combination, is a hydrocarbon ring containing from 3 to 8 carbon atoms; aryl, alone or in combination, means a phenyl or naphthyl radical optionally substituted with alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano or haloalkyl radicals; heterocyclyl or heterocycloalkyl means a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having one or more nitrogen, oxygen or sulphur heteroatoms, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy or oxo radicals, or on a secondary nitrogen atom by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl radicals, or on a tertiary nitrogen atom by oxido radical; and heteroaryl means an aromatic heterocyclyl radical which is optionally substituted as defined above with respect to the definition of heterocyclyl;
wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycrbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically acceptable salt, ester, prodrug thereof.

6. Compound of claim 5 wherein P^1 represents alkoxycarbonyl, aralkyloxycarbonyl, heteroaralkoxycarbonyl, aroyl, heteroaroyl, alkanoyl or cycloalkanoyl radicals;

R^2 represents alkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with halogen, $-OR^9$ or $-SR^9$ radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, cycloalkyl or cycloalkylalkyl radicals; and
R^4 represents alkyl, aryl or heteroaryl radicals.

7. Compound of claim 6 wherein P^1 represents 3-pyridylmethyloxycarbonyl, 3-pyridylmethyloxycarbonyl N-oxide, 4-pyridylmethyloxycarbonyl, 4-pyridylmethyloxycarbonyl N-oxide, 5-pyrimidylmethyloxycarbonyl, tert-butyloxycarbonyl, allyloxycarbonyl, 2-propyloxycarbonyl, benzyloxycarbonyl, cycloheptylcarbonyl, cyclohexylcarbonyl, cyclopentylcarbonyl, benzoyl, 2-substituted benzoyl, 4-pyridylcarbonyl, 2-methylbenzoyl, 3-methylbenzoyl, 4-methylbenzoyl, 2-chlorobenzoyl, 2-ethylbenzoyl, 2,6-dimethylbenzoyl, 2,3-dimethylbenzoyl, 2,4-dimethylbenzoyl or 2,5-dimethylbenzoyl radicals;

R^2 represents benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, paramethoxybenzyl, isobutyl or

n-butyl radicals;
R^3 represnts isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl or n-propyl radicals; and R^4 represents phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl or 4-pyridyl N-oxide radicals.

8. Compound of claim 5 wherein P^1 represents heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or heteroaroyl radicals;

R^2 represents alkyl, cycloalkylalkyl or aralkyl radicals, which radicals are optionally substituted with halogen, $-OR^9$ or $-SR^9$ radicals, wherein R^9 represents hydrogen or alkyl radicals;
R^3 represents alkyl, cycloalkyl or cycloalkylalkyl radicals; and
R^4 represents alkyl, aryl or heteroaryl radicals; and

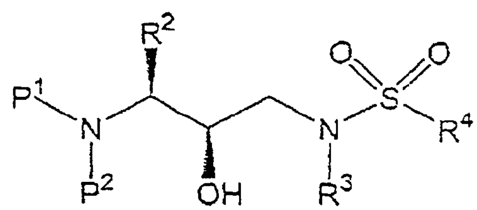
wherein heterocyclyl or heterocycloalkyl means a 5-6 ring membered heterocycle or a benzfused 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms; and heteroaryl means an aromatic 5-6 ring membered heterocycle or an aromatic benzfused 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms.

9. Compound of claim 8 wherein P^1 represents heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl or heteroaroyl radicals;

R^2 represents benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, paramethoxybenzyl, isobutyl or n-butyl radicals;
R^3 represents isobutyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl or n-propyl radicals; and

wherein heterocyclyl or heterocycloalkyl means a 5-6 ring membered heterocyle having one or two nitrogen, oxygen or sulphur heteroatoms; and heteroaryl means an aromatic 5-6 ring membered heterocycle having one or two nitrogen, oxygen or sulphur heteroatoms.

10. A retroviral protease inhibiting compound according to claim 1 having the formula



wherein:

P^1 represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkanoyl, heterocyclylalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxycarbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

P^2 represents hydrogen;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, $-NO_2$, $-C\equiv N$. CF_3, $-OR^9$, $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and

R^4 represents radicals as defined by R^3 except for hydrogen;

wherein aryl wherever occuring may optionally carry one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl;
wherein heterocycle or heteroaryl may optionally be substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo and/or on a secondary nitrogen atom by alkyl, aralkoxycrbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom by oxido and which is attached via a carbon atom;
and the pharmaceutically acceptable salt, prodrug or ester thereof.

11. Compound of Claim 10 wherein

R^2 represents cycloalkylalkyl, aralkyl, alkyl, benzyl, cyclohexylmethyl, 2-naphthylmethyl, para-fluorobenzyl, para-methoxybenzyl, isobutyl, or n-butyl;

R^3 represents alkyl, cycloalkyl, cycloalkylalkyl, isobmyl, isoamyl, cyclohexyl, cyclohexylmethyl, n-butyl, or n-propyl; and

R^4 represents aryl, alkyl, aryl, para-substituted aryl, heteroaryl, phenyl, para-methoxyphenyl, para-cyanophenyl, para-chlorophenyl, para-hydroxyphenyl, para-nitrophenyl, para-fluorophenyl, 2-naphthyl, 3-pyridyl, 3-pyridyl N-oxide, 4-pyridyl, or 4-pyridyl N-oxide.

12. A pharmaceutical composition comprising a compound of any of claims 1-11 and a pharmaceutically acceptable carrier.

13. Use of a composition of claim 12 for preparing a medicament for inhibiting a retroviral protease.

14. Use according to claim 13 wherein the retroviral protease is HIV protease.

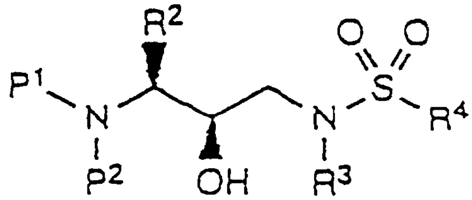
15. Use of a composition of claim 12 for preparing a medicament for treating a retroviral infection.

16. Use according to claim 15 wherein the retroviral infection is an HIV infection.

17. Use of a composition of claim 12 for preparing a medicament for treating AIDS.

Patentansprüche

1. Eine Verbindung dargestellt durch die Formel



(I)

worin

P^1 und P^2 unabhängig voneinander Wasserstoff, Reste von Alkoxycarbonyl, Aralkoxycarbonyl, Alkylcarbonyl, Cycloalkylcarbonyl, Cycloalkylalkoxycarbonyl, Cycloalkylalkanoyl, Alkanoyl, Aralkanoyl, Aroyl, Aryloxycarbonyl, Aryloxycarbonylalkyl, Aryloxyalkanoyl, Hetreocyclylcarbonyl, Heterocyclyloxycarbonyl, Heterocyclylalkanoyl, Heterocyclylalkoxycarbonyl, Heteroaralkanoyl, Heteroaralkoxcarbonyl, Heteroaryloxycarbonyl, Heteroaroyl, Alkyl, Alkenyl, Cycloalkyl, Aryl, Aralkyl, Aryloxyalkyl, Heteroaryloxyalkyl, Hydroxyalkyl, Aminocarbonyl, Aminoalkanoyl und mono- und disubstituiertes Aminocarbonyl und mono- und disubstituiertes Aminoalkanoyl bedeuten, worin die Substituenten ausgewählt sind aus Alkyl, Aryl, Aralkyl, Cycloalkyl, Cycloalkylalkyl, Heteroaryl, Heteroaralkyl, Heterocycloalkyl, Heterocycloalkylalkyl oder worin dieser Aminoalkanoylrest disubstituiert ist, wobei diese Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocycloalkyl- oder Heteroarylrest bilden;

R^2 Reste wie Alkyl, Aryl, Cycloalkyl, Cycloalkylalkyl und Aralkyl bedeutet, wobei die Reste gegebenenfalls substituiert sind mit einer Gruppe ausgewählt aus Alkyl- und Halogenresten, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, worin R^9 Wasserstoff oder Alkylreste bedeutet;

R^3 Wasserstoff bedeutet oder Reste von Alkyl, Haloalkyl, Alkenyl, Alkinyl, Hydroxyalkyl, Alkoxyalkyl, Cycloalkyl, Cycloalkylalkyl, Heterocycloalkyl, Heteroaryl, Heterocycloalkylalkyl, Aryl, Aralkyl, Heteroaralkyl, Aminoalkyl und mono- und disubstituierte Aminoalkylreste, wobei diese Substituenten ausgewählt sind aus Resten von Alkyl, Aryl, Aralkyl, Cycloalkyl, Cycloalkylalkyl, Heteroaryl, Heteroaralkyl, Heterocycloalkyl und Heterocycloalkylalkylresten oder im Falle eines disubstituierten Aminoalkylrestes diese Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocycloalkyl- oder Heteroarylrest bilden und

R^4 Reste bedeutet wie durch R^3 definiert, außer Wasserstoff;

worin Aryl, wo immer es vorkommt, gegebenenfalls einen oder mehrere Substituenten tragen kann ausgewählt aus Alkyl, Alkoxy, Halogen, Hydroxy, Amino, Nitro, Cyano, Haloalkyl;
worin Heterocycel oder Heteroaryl gegebenenfalls substituiert sein können an einem oder mehreren Kohlenstoffatomen durch Halogen, Alkyl, Alkoxy, Oxo und/oder einem sekundären Stickstoffatom durch Alkyl, Aralkoxycarbonyl, Alkanoyl, Phenyl oder Phenylalkyl oder an einem tertiären Stickstoffatom durch Oxido, welches gebunden ist über ein Kohlenstoffatom;
und deren pharmazeutisch verträgliche Salze, Ester oder Proarzneimittel.

2. Verbindung des Anspruchs 1, worin

R^2 Cycloalkylalkyl, Aralkyl, Alkyl, Benzyl, Cyclohexylmethyl, 2-Naphthylmethyl, para-Fluorbenzyl, para-Methoxybenzyl, Isobutyl oder n-Butyl bedeutet;

R^3 Alkyl, Cycloalkyl, Cycloalkylalkyl, Isobutyl, Isoamyl, Cyclohexyl, Cyclohexylmethyl, n-Butyl oder n-Propyl bedeutet und

R^4 Aryl, Alkyl, Aryl, para-substituiertes Aryl, Heteroaryl, Phenyl, para-Methoxyphenyl, para-Cyanophenyl, para-Chlorphenyl, para-Hydroxyphenyl, para-Nitrophenyl, para-Fluorphenyl, 2-Naphthyl, 3-Pyridyl, 3-Pyridyl N-oxid, 4-Pyridyl oder 4-Pyridyl N-oxid.

3. Verbindung des Anspruchs 1, worin P^1 und P^2 unabhängig voneinander Wasserstoff, Alkoxycarbonyl, Aralkyloxycarbonyl, Heteroaralkoxycarbonyl, Aroyl, Heteroaroyl, Alkanoyl, Cycloalkanoyl, 3-Pyridylmethyloxycarbonyl, 3-Pyridylmethyloxycarbonyl N-oxid, 4-Pyridylmethyloxycarbonyl, 4-Pyridylmethyloxycarbonyl N-oxid, 5-Pyrimidylmethyloxycarbonyl, tert-Butyloxycarbonyl, Allyloxycarbonyl, 2-Propyloxycarbonyl, Benzyloxycarbonyl, Cycloheptylcarbonyl, Cyclohexylcarbonyl, Cyclopentylcarbonyl, Benzoyl, 2-substituiertes Benzoyl, 4-Pyridylcarbonyl, 2-Methylbenzoyl, 3-Methylbenzoyl, 4-Methylbenzoyl, 2-Chlorbenzoyl, 2-Ethylbenzoyl, 2,6-Dimethylbenzoyl, 2,3-Dimethylbenzoyl, 2,4-Dimethylbenzoyl oder 2,5-Dimethylbenzoyl bedeuten;

R^2 Cycloalkylalkyl, Aralkyl, Alkyl, Benzyl, Cyclohexylmethyl, 2-Naphthylmethyl, para-Fluorbenzyl, para-Methoxybenzyl, Isobutyl oder n-Butyl bedeutet;

R^3 Alkyl, Cycloalkyl, Cycloalkylalkyl, Isobutyl, Isoamyl, Cyclohexyl, Cyclohexylmethyl, n-Butyl oder n-Propyl bedeutet und

R^4 Aryl, Alkyl und Heteroaryl, Aryl, para-substituiertes Aryl, Phenyl, para-Methoxyphenyl, para-Cyanophenyl, para-Chlorphenyl, para-Hydroxyphenyl, para-Nitrophenyl, para-Fluorphenyl, 2-Napththyl, 3-Pyridyl, 3-Pyridyl N-oxid, 4-Pyridyl oder 4-Pyridyl N-oxid bedeutet.

4. Eine Verbindung des Anspruchs 1 und zwar;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(phenylmethyl) propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl) (4-fluorphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl) (4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl)(4-chlorphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl)(4-acetamidophenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl[2R-hydroxy-3-[(2-methylpropyl)(4-aminophenylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (4-methoxyphenysulfonyl) amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (4-fluorphenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl)(4-nitrophenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (4-chlorphenylsulfonyl) amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl)(4-methoxyphenylsulfonyl) amino]-1S-(4-fluorphenylmethyl) propyl]carbamat;

Phenylmethyl [2R-hydroxy-3-[(2-methylpropyl)(4-fluorphenylsulfonyl)amino]-1S-(4-fluorphenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(butyl)(phenylsulfonyl) amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl[2R-hydroxy-3-[(cyclohexylmethyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamat;

Phenylmethyl[2R-hydroxy-3-[(cyclohexyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl] carbamat;

Phenylmethyl [2R-hydroxy-3-[(propyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamat;

Pentanamid, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(3-methylpropyl)(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

Pentanamid, 2S-[[(methylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

Pentanamid, 2S-[[(dimethylamino)acetyl]amino]-N-2R-hydroxy-3-[(4-methylbutyl)(phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]-3S-methyl;

[2R-Hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamin;

2R-Hydroxy-3-[(2-methylpropyl)(4-hydroxyphenyl)sulfonyl]amino-1S-(phenylmethyl)propylamin;

[2R-Hydroxy-3-[(phenylsulfonyl)(3-methylbutyl)amino]-1S-(phenylmethyl)propylamin;

[2R-Hydroxy-3-[(phenylsulfonyl) (2-methylpropyl)amino]-1S-(phenylmethyl)propylamin;

[2R-Hydroxy-3-[(phenylsulfonyl)(cyclohexylmethyl)amino]-1S-(phenylmethyl)propylamin;

[2R-Hydroxy-3-[(phenylsulfonyl) (cyclohexyl)amino]-1S-(phenylmethyl)propylamin;

4-Pyridincarboxamid,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl];

Benzamid,
N-[2R-Hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2,6-dimethyl;

Benzamid,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-methyl;

Benzamid,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-ethyl;

Benzamid,
N-[2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2-chlor;

Carbaminsäure, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbaminsäure, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl] (2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridyimethyl ester, N-oxid;

Carbaminsäure, [2R-hydroxy-3-[[phenylsulfonyl](2-methylpropyl)amino-]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbaminsäure, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester;

Carbaminsäure, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 4-pyridylmethyl ester, N-oxid;

Carbaminsäure, [2R-hydroxy-3-[[(4-chlorphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

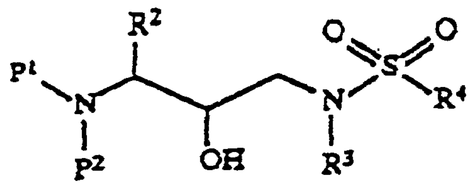
Carbaminsäure, [2R-hydroxy-3-[[(4-nitrophenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbaminsäure, [2R-hydroxy-3-[[(4-fluorphenyl)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester;

Carbaminsäure, [2R-hydroxy-3-[[(4-hydroxyphenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-, 3-pyridylmethyl ester

Carbaminsäure, [2R-hydroxy-3-[[(4-methoxyphenyl)sulfonyll(2-methylpropyl)aminol-1S-(phenylmethyl)propyl]-, 5-pyrimidylmethyl ester.

5. Eine Verbindung der Formel



worin

P^1 Reste wie Alkoxycarbonyl, Aralkoxycarbonyl, Alkanoyl, Cycloalkylcarbonyl, Cycloalkylalkoxycarbonyl, Cycloalkylalkanoyl, Aralkanoyl, Aroyl, Aryloxycarbonyl, Heterocyclylcarbonyl, Heterocyclyloxycarbonyl, Heteroyclylalkoxycarbonyl, Heteroaralkoxycarbonyl, Heteroaryloxycarbonyl oder Heteroaroyl bedeutet;
P^2 Wasserstoff bedeutet;
R^2 Reste wie Alkyl, Aryl, Cycloalkyl, Cycloalkylalkyl oder Aralkyl bedeutet, wobei diese Reste gegebenenfalls substituiert sind mit Resten wie Alkyl, Halogen, $-NO_2$, -CN, CF_3, $-OR^9$ oder SR^9, worin R^9 Wasserstoff oder Alkylreste bedeutet;
R^3 Reste wie Alkyl, Alkenyl, Alkinyl, Hydroxyalkyl, Alkoxyalkyl, Cycloalkyl, Cycloalkylalkyl, Heterocyclyl, Heteroaryl, Heterocyclylalkyl, Aryl, Aralkyl oder Heteroaralkyl bedeutet und
R^4 Reste wie Alkyl, Haloalkyl, Alkenyl, Alkinyl, Cycloalkyl, Heterocycloalkyl, Heteroaryl, Aryl oder Aralkyl bedeutet und

worin Alkyl, allein oder in Kombination, ein geradkettiger oder verzweigtkettiger Kohlenwasserstoffrest ist mit eins bis acht Kohlenstoffatomen; Alkenyl, allein oder in Kombination, einen geradkettigen oder verzweigtkettigen Kohlenwasserstoffrest mit einem oder mehreren Doppelbindungen und von zwei bis acht Kohlenstoffatomen; Alkinyl, allein oder in Kombination, einen geradkettigen Kohlenwasserstoffrest bedeutet, mit einer oder mehreren Dreifachbindungen und mit zwei bis zehn Kohlenstoffatomen; Cycloalkyl, allein oder in Kombination, einen Kohlenwasserstoffring bedeutet, enthaltend drei bis acht Kohlenstoffatome; Aryl, allein oder in Kombination, einen Phenyl- oder Naphthylrest bedeutet, gegebenenfalls substituiert mit Resten wie Alkyl, Alkoxy, Halogen, Hydroxy, Amino, Nitro, Cyano oder Haloalkyl; Heterocyclyl oder Heterocycloalkyl einen gesättigten oder teilweise ungesättigten monocyclischen, bicyclischen oder tricyclischen Heterocycel bedeutet mit einem oder mehreren Stickstoff-, Sauerstoff- oder Schwefelheteroatomen, der gegebenenfalls substituiert ist an einem oder mehreren Kohlenstoffatomen durch Reste wie Halogen, Alkyl, Alkoxy oder Oxo oder an einem sekundären Stickstoffatom durch Reste wie Alkyl, Aralkoxycarbonyl, Alkanoyl, Phenyl oder Phenylalkyl oder an einem tertiären Stickstoffatom durch Oxidoreste und Heteroaryl bedeutet einen aromatischen Heterocyclylrest, der gegebenenfalls substituiert ist, wie vorstehend definiert, mit Bezug auf die Definition von Heterocyclyl;
worin Aryl, wo immer es vorkommt, gegebenenfalls einen oder mehrere Substituenten tragen kann ausgewählt aus Alkyl, Alkoxy, Halogen, Hydroxy, Amino, Nitro, Cyano, Haloalkyl;
worin Heterocycel oder Heteroaryl gegebenenfalls substituiert sein kann an einem oder mehreren Kohlenstoffatomen durch Halogen, Alkyl, Alkoxy, Oxo und/oder an einem sekundären Stickstoffatom durch Alkyl, Aralkoxycarbonyl, Alkanoyl, Phenyl oder Phenylalkyl oder an einem tertiären Stickstoffatom durch Oxido und welcher angelagert ist an einem Kohlenstoffatom
und deren pharmazeutisch verträgliches Salz, Ester, Proarzneimittel.

6. Verbindung des Anspruchs 5, worin P^1 Reste wie Alkoxycarbonyl, Aralkyloxycarbonyl, Heteroaralkoxycarbonyl, Aroyl, Heteroaroyl, Alkanoyl oder Cycloalkanoyl bedeutet;

R^2 Reste wie Alkyl, Cycloalkylalkyl oder Aralkyl bedeutet, wobei diese Reste gegebenenfalls substituiert sind mit Resten wie Halogen, $-OR^9$ oder $-SR^9$, worin R^9 Wasserstoff oder Alkylreste bedeutet;
R^3 Reste wie Alkyl, Cycloalkyl oder Cycloalkylalkyl bedeutet und
R^4 Reste wie Alkyl, Aryl oder Heteroaryl bedeutet.

7. Verbindung des Anspruchs 6, worin P^1 einen Rest wie 3-Pyridylmethyloxycarbonyl, 3-Pyridylmethyloxycarbonyl N-oxid, 4-Pyridylmethyloxycarbonyl, 4-Pyridylmethyloxycarbonyl N-oxid, 5-Pyrimidylmethyloxycarbonyl, tert-Butyloxycarbonyl, Allyloxycarbonyl, 2-Propyloxycarbonyl, Benzyloxycarbonyl, Cycloheptylcarbonyl, Cyclohexylcarbonyl, Cyclopentylcarbonyl, Benzoyl, 2-substituiertes Benzoyl, 4-Pyridylcarbonyl, 2-Methylbenzoyl, 3-Methylbenzoyl, 4-Methylbenzoyl, 2-Chlorbenzoyl, 2-Ethylbenzoyl, 2,6-Dimethylbenzoyl, 2,3-Dimethylbenzoyl, 2,4-Dimethylbenzoyl oder 2,5-Dimethylbenzoyl bedeutet;

    R^2 einen Rest wie Benzyl, Cyclohexylmethyl, 2-Naphthylmethyl, para-Fluorbenzyl, para-Methoxybenzyl, Isobutyl oder n-Butyl bedeutet;
    R^3 einen Rest wie Isobutyl, Isoamyl, Cyclohexyl, Cyclohexylmethyl, n-Butyl oder n-Propyl bedeutet und R^4 einen Rest wie Phenyl, para-Methoxyphenyl, para-Cyanophenyl, para-Chlorphenyl, para-Hydroxyphenyl, para-Nitrophenyl, para-Fluorphenyl, 2-Naphthyl, 3-Pyridyl, 3-Pyridyl N-oxid, 4-Pyridyl oder 4-Pyridyl N-oxid bedeutet.

8. Verbindung des Anspruchs 5, worin P^1 einen Rest wie Heterocyclylcarbonyl, Heterocyclyloxycarbonyl, Heterocyclylalkoxycarbonyl, Heteroaralkoxycarbonyl, Heteroaryloxycarbonyl oder Heteroaroyl bedeutet;

    R^2 einen Rest wie Alkyl, Cycloalkylalkyl oder Aralkyl bedeutet, wobei die Reste gegebenenfalls substituiert sind mit einem Rest wie Halogen, -OR^9 oder -SR^9, worin R^9 Wasserstoff oder Alkylreste bedeutet;
    R^3 Reste wie Alkyl, Cycloalkyl oder Cycloalkylalkyl bedeutet und
    R^4 Reste wie Alkyl, Aryl oder Heteroaryl bedeutet und

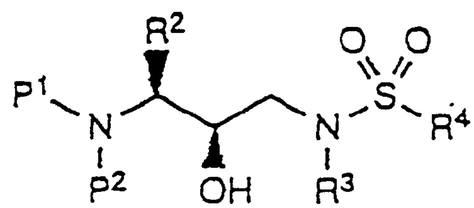
    worin Heterocyclyl oder Heterocycloalkyl einen 5-6 ringgliedrigen Heterocycel oder einen Benz kondensierten 5-6 ringgliedrigen Heterocycel bedeutet mit einem oder zwei Stickstoff-, Sauerstoff- oder Schwefelheteroatomen oder Heteroaryl einen aromatischen 5-6 ringgliedrigen Heterocycel oder einen aromatischen Benz kondensierten 5-6 ringgliedrigen Heterocycel bedeutet mit einem oder zwei Stickstoff-, Sauerstoff- oder Schwefelheteroatomen.

9. Verbindung des Anspruchs 8, worin P^1 einen Rest wie Heterocyclylcarbonyl, Heterocyclyloxycarbonyl, Heterocyclylalkoxycarbonyl, Heteroaralkoxycarbonyl, Heteroaryloxycarbonyl oder Heteroaroyl bedeutet;

    R^2 Reste wie Benzyl, Cyclohexylmethyl, 2-Naphthylmethyl, para-Fluorbenzyl, para-Methoxybenzyl, Isobutyl oder n-Butyl bedeutet;
    R^3 einen Rest wie Isobutyl, Isoamyl, Cyclohexyl, Cyclohexylmethyl, n-Butyl oder n-Propyl bedeutet und

    worin Heterocyclyl oder Heterocycloalkyl einen 5-6 ringgliedrigen Heterocycel bedeutet mit einem oder zwei Stickstoff-, Sauerstoff- oder Schwefelheteroatomen und Heteroaryl einen aromatischen 5-6 ringgliedrigen Heterocycel bedeutet mit einem oder zwei Stickstoff-, Sauerstoffoder Schwefelheteroatomen.

10. Eine retrovirale Protease inhibierende Verbindung gemäß Anspruch 1 der Formel



worin

    P^1 einen Rest wie Alkoxycarbonyl, Aralkoxycarbonyl, Alkylcarbonyl, Cycloalkylcarbonyl, Cycloalkylalkoxycarbonyl, Cycloalkylalkanoyl, Alkanoyl, Aralkanoyl, Aroyl, Aryloxycarbonyl, Aryloxycarbonylalkyl, Aryloxyalkanoyl, Heterocyclylcarbonyl, Heterocyclyloxycarbonyl, Heterocyclylalkanoyl, Heterocyclylalkoxycarbonyl, Heteroaralkanoyl, Heteroaralkoxycarbonyl, Heteroaryloxycarbonyl, Heteroaroyl, Alkyl, Alkenyl, Cycloalkyl, Aryl, Aralkyl, Aryloxyalkyl, Heteroaryloxyalkyl, Hydroxyalkyl, Aminocarbonyl, Aminoalkanoyl und mono- und disubstituiertes Aminocarbonyl und mono- und disubstituiertes Aminoalkanoyl bedeutet, worin die Substituenten

ausgewählt sind aus Alkyl, Aryl, Aralkyl, Cycloalkyl, Cycloalkylalkyl, Heteroaryl, Heteroaralkyl, Heterocycloalkyl, Heterocycloalkylalkyl oder wo diese Aminoalkanoylreste disubstituiert sind, wobei die Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen Heterocycloalkyl- oder Heteroarylrest bilden

P^2 Wasserstoff bedeutet;

R^2 einen Rest wie Alkyl, Aryl, Cycloalkyl, Cycloalkylalkyl und Aralkyl bedeutet, wobei die Reste gegebenenfalls substituiert sind mit einer Gruppe ausgewählt aus Alkyl und Halogenresten, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, worin R^9 Wasserstoff und Alkylreste bedeutet;

R^3 Reste wie Wasserstoff, Alkyl, Haloalkyl, Alkenyl, Alkinyl, Hydroxyalkyl, Alkoxyalkyl, Cycloalkyl, Cycloalkylalkyl, Heterocycloalkyl, Heteroaryl, Heterocycloalkylalkyl, Aryl, Aralkyl, Heteroaralkyl, Aminoalkyl und mono- und disbustituierte Aminoalkylreste bedeutet, worin diese Substituenten ausgewählt sind aus Resten wie Alkyl, Aryl, Aralkyl, Cycloalkyl, Cycloalkylalkyl, Heteroaryl, Heteroaralkyl, Heterocycloalkyl und Heterocycloalkylalkylresten und im Falle eines disbustituierten Aminoalkylrestes bilden diese Substituenten zusammen mit dem Stickstoffatom, an das sie gebunden sind einen Heterocycloalkyl- oder Heteroarylrest und

R^4 bedeutet Reste wie durch R^3 definiert, außer Wasserstoff;

worin Aryl, wo immer es vorkommt, gegebenenfalls einen oder mehrere Substituenten tragen kann ausgewählt aus Alkyl, Alkoxy, Halogen, Hydroxy, Amino, Nitro, Cyano, Haloalkyl;
worin Heterocycel oder Heteroaryl gegebenenfalls substituiert sein kann an einem oder mehreren Kohlenstoffatomen durch Halogen, Alkyl, Alkoxy, Oxo und/oder an einem sekundären Stickstoffatom durch Alkyl, Aralkoxycarbonyl, Alkanoyl, Phenyl oder Phenylalkyl oder an einem tertiären Stickstoffatom durch Oxido und welches über ein Kohlenstoffatom gebunden ist,
und das pharmazeutisch verträgliche Salz, Vorarzneimittel oder Ester davon.

11. Verbindung des Anspruchs 10, worin

R^2 Cycloalkylalkyl, Aralkyl, Alkyl, Benzyl, Cyclohexylmethyl, 2-Naphthylmethyl, para-Fluorbenzyl, para-Methoxybenzyl, Isobutyl, oder n-Butyl bedeutet;

R^3 Alkyl, Cycloalkyl, Cycloalkylalkyl, Isobutyl, Isoamyl, Cyclohexyl, Cyclohexylmethyl, n-Butyl oder n-Propyl bedeutet und

R^4 Aryl, Alkyl, Aryl, para-substituiertes Aryl, Heteroaryl, Phenyl, para-Methoxyphenyl, para-Cyanophenyl, para-Chlorphenyl, para-Hydroxyphenyl, para-Nitrophenyl, para-Fluorphenyl, 2-Napththyl, 3-Pyridyl, 3-Pyridyl N-oxid, 4-Pyridyl oder 4-Pyridyl N-oxid bedeutet.

12. Eine pharmazeutische Zusammensetzung, enthaltend eine Verbindung von einem der Ansprüche 1-11 und einen pharmazeutisch verträglichen Träger.

13. Verwendung einer Zusammensetzung des Anspruchs 12 zur Herstellung eines Medikamentes zur Inhibierung einer retroviralen Protease.

14. Verwendung gemäß Anspruch 13, worin die retrovirale Protease HIV-Protease ist.

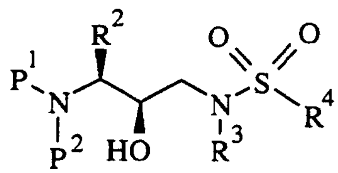
15. Verwendung einer Zusammensetzung des Anspruchs 12 zur Herstellung eines Medikamentes zur Behandlung einer retroviralen Infektion.

16. Verwendung gemäß Anspruch 15, worin die retrovirale Infektion eine HIV-Infektion ist.

17. Verwendung einer Zusammensetzung des Anspruchs 12 zur Herstellung eines Medikaments zur Behandlung von AIDS.

Revendications

1. Composé représenté par la formule :



(I)

dans laquelle :

P^1 et P^2 représentent, de façon indépendante, un hydrogène, des radicaux alcoxycarbonyle, aralcoxycarbonyle, alkylcarbonyle, cycloalkylcarbonyle, cycloalkylalcoxycarbonyle, cycloalkylalcanoyle, alcanolyle, aralcanoyle, aroyle, aryloxycarbonyle, aryloxycarbonylalkyle, aryloxyalcanoyle, hétérocyclylcarbonyle, hétérocyclyloxycarbonyle, hétérocyclylalcanoyle, hétérocyclylalcoxycarbonyle, hétéroaralcanoyle, hétéroaralcoxycarbonyle, hétéroaryloxycarbonyle, hétéroaroyle, alkyle, alcényle, cycloalkyle, aryle, aralkyle, aryloxyalkyle, hétéroaryloxyalkyle, hydroxyalkyle, aminocarbonyle, aminoalcanoyle et aminocarbonyle mono- et disubstitué et aminoalcanoyle mono- et disubstitué, les substituants étant choisis parmi les radicaux alkyle, aryle, aralkyle, cycloalkyle, cycloalkylalkyle, hétéroaryle, hétéroaralkyle, hétérocycloalkyle, hétérocycloalkylalkyle, ou, quand ledit radical aminoalcanoyle est disubstitué, lesdits substituants forment, avec l'atome d'azote auquel ils sont rattachés, un radical hétérocycloalkyle ou hétéroaryle ;
R^2 représente des radicaux alkyle, aryle, cycloalkyle, cycloalkylalkyle et aralkyle, radicaux éventuellement substitués par un groupe choisi parmi les radicaux alkyle et halogène, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, où R^9 représente l'hydrogène et des radicaux alkyle ;
R^3 représente l'hydrogène, des radicaux alkyle, halogénoalkyle, alcényle, alcynyle, hydroxyalkyle, alcoxyalkyle, cycloalkyle, cycloalkylalkyle, hétérocycloalkyle, hétéroaryle, hétérocycloalkylalkyle, aryle, aralkyle, hétéroaralkyle, aminoalkyle et aminoalkyle mono- et disubstitués, lesdits substituants étant choisis parmi les radicaux alkyle, aryle, aralkyle, cycloalkyle, cycloalkylalkyle, hétéroaryle, hétéroaralkyle, hétérocycloalkyle et hétérocycloalkylalkyle, ou, dans le cas d'un radical aminoalkyle disubstitué, lesdits substituants formant, avec l'atome d'azote auquel ils sont rattachés, un radical hétérocycloalkyle ou un radical hétéroaryle ; et
R^4 représente les radicaux tels que définis pour R^3, exception faite de l'hydrogène ;

où les radicaux aryle, quelle que soit leur position, peuvent éventuellement porter un ou plusieurs substituants choisis parmi alkyle, alcoxy, halogène, hydroxy, amino, nitro, cyano, halogénoalkyle ;
où les radicaux hétérocyclyle ou hétéroaryle peuvent éventuellement être substitués sur un ou plusieurs atomes de carbone par halogène, alkyle, alcoxy, oxo et/ou sur un atome d'azote secondaire par alkyle, aralcoxycarbonyle, alcanoyle, phényle ou phénylalkyle ou sur un atome d'azote tertiaire par oxydo et qui sont attachés par l'intermédiaire d'un atome de carbone ;
et ses sels, esters ou précurseurs de médicaments pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel :

R^2 représente des radicaux cycloalkylalkyle, aralkyle, alkyle, benzyle, cyclohexylméthyle, 2-naphtylméthyle, para-fluorobenzyle, para-méthoxybenzyle, isobutyle ou n-butyle ;
R^3 représente des radicaux alkyle, cycloalkyle, cycloalkylalkyle, isobutyle, isoamyle, cyclohexyle, cyclohexylméthyle, n-butyle ou n-propyle ; et
R^4 représente des radicaux aryle, alkyle, aryle, aryle para-substitué, hétéroaryle, phényle, para-méthoxyphényle, para-cyanophényle, para-chlorophényle, para-hydroxyphényle, para-nitrophényle, para-fluorophényle, 2-naphtyle, 3-pyridyle, N-oxyde de 3-pyridyle, 4-pyridyle ou N-oxyde de 4-pyridyle.

3. Composé selon la revendication 1, dans lequel P^1 et P^2 représentent, de façon indépendante, un hydrogène, des radicaux alcoxycarbonyle, aralcoxycarbonyle, hétéroaralcoxycarbonyle, aroyle, hétéroaroyle, alcanoyle, cycloalcanoyle, 3-pyridylméthyloxycarbonyle, N-oxyde de 3-pyridylméthyloxycarbonyle, 4-pyridylméthyloxycarbonyle, N-oxyde de 4-pyridylméthyloxycarbonyle, 5-pyrimidylméthyloxycarbonyle, tert-butyloxycarbonyle, allyloxycarbonyle,

2-propyloxycarbonyle, benzyloxycarbonyle, cycloheptylcarbonyle, cyclohexylcarbonyle, cyclopentylcarbonyle, benzoyle, benzoyle substitué en 2, 4-pyridylcarbonyle, 2-méthylbenzoyle, 3-méthylbenzoyle, 4-méthylbenzoyle, 2-chlorobenzoyle, 2-éthylbenzoyle, 2,6-diméthylbenzoyle, 2,3-diméthylbenzoyle, 2,4-diméthylbenzoyle ou 2,5-diméthylbenzoyle ;

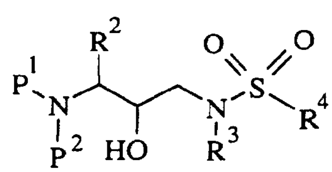
R^2 représente des radicaux cycloalkylalkyle, aralkyle, alkyle, benzyle, cyclohexylméthyle, 2-naphtylméthyle, para-fluorobenzyle, para-méthoxybenzyle, isobutyle ou n-butyle ;
R^3 représente des radicaux alkyle, cycloalkyle, cycloalkylalkyle, isobutyle, isoamyle, cyclohexyle, cyclohexylméthyle, n-butyle ou n-propyle ; et
R^4 représente des radicaux aryle, alkyle et hétéroaryle, aryle, aryle para-substitué, phényle, para-méthoxyphényle, para-cyanophényle, para-chlorophényle, para-hydroxyphényle, para-nitrophényle, para-fluorophényle, 2-naphtyle, 3-pyridyle, N-oxyde de 3-pyridyle, 4-pyridyle ou N-oxyde de 4-pyridyle.

4. Composé selon la revendication 1, qui est

le [2R-hydroxy-3-[(2-méthylpropyl)(phénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-méthoxyphénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-fluorophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-nitrophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-chlorophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-acétamidophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-aminophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(3-méthylbutyl)(4-méthoxyphénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(3-méthylbutyl)(4-fluorophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(3-méthylbutyl)(4-nitrophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(3-méthylbutyl)(4-chlorophénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-méthoxyphénylsulfonyl)amino-1S-(4-fluorophénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(2-méthylpropyl)(4-fluorophénylsulfonyl)amine-1S-(4-fluorophénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(butyl)(phénylsulfonyl)amine-1S-(phénylméthyl)propyl]-carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(cyclohexylméthyl)(phénylsulfonyl)amine-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(cyclohexyl)(phénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le [2R-hydroxy-3-[(propyl)(phénylsulfonyl)amino-1S-(phénylméthyl)propyl]carbamate de phénylméthyle ;
le 2S-[[(diméthylamino)acétyl]amino]-N-2R-hydroxy-3-[(3-méthylpropyl)-(4-méthoxyphénylsulfonyl)amino]-1S-(phénylméthyl)propyl]-3S-méthylpentanamide ;
le 2S-[[(méthylamino)acétyl]amino]-N-2R-hydroxy-3-[(4-méthylbutyl)-(phénylsulfonyl)amine]-1S-(phénylméthyl)propyl]-3S-méthylpentanamide ;
le2S-[[(diméthylamino)acétyl]amino]-N-2R-hydroxy-3-[(4-méthylbutyl)-(phénylsulfonyl)amine]-1S-(phénylméthyl)propyl]-3S-méthylpentanamide ;
la [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propylamine ;
la [2R-hydroxy-3-[(2-méthylpropyl)(4-hydroxyphényl)sulfonyl]amine-1S-(phénylméthyl)propylamine ;
la [2R-hydroxy-3-[(phénylsulfonyl)(3-méthylbutyl)amine]-1S-(phénylméthyl)propylamine ;
la [2R-hydroxy-3-[(phénylsulfonyl)(2-méthylpropyl)amine]-1S-(phénylméthyl)propylamine ;
la [2R-hydroxy-3-[(phénylsulfonyl)(cyclohexylméthyl)amine]-1S-(phénylméthyl)propylamine ;
la [2R-hydroxy-3-[(phénylsulfonyl)(cyclohexyl)amine]-1S-(phénylméthyl)propylamine ;

le N-[2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amine]-1S-(phénylméthyl)propyl]pyridine-4-carboxamide ;
le N-[2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amine]-1S-(phénylméthyl)propyl]-2,6-diméthylbenzamide ;
le N-[2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amine]-1S-(phénylméthyl)propyl]-2-méthylbenzamide ;
le N-[2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]-2-éthylbenzamide ;
le N-[2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]-2-chlorobenzamide ;
l'acide [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle, N-oxyde ;
l'acide [2R-hydroxy-3-[[phénylsulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 4-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 4-pyridylméthyle, N-oxyde ;
l'acide [2R-hydroxy-3-[[(4-chlorophényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-nitrophényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-fluorophényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ;
l'acide [2R-hydroxy-3-[[(4-hydroxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 3-pyridylméthyle ; ou
l'acide [2R-hydroxy-3-[[(4-méthoxyphényl)sulfonyl](2-méthylpropyl)amino]-1S-(phénylméthyl)propyl]carbamique, ester de 5-pyrimidylméthyle.

5. Composé représenté par la formule :



dans laquelle :

P^1 représente des radicaux alcoxycarbonyle, aralcoxycarbonyle, alcanoyle, cycloalkylcarbonyle, cycloalkylalcoxycarbonyle, cycloalkylalcanoyle, aralcanoyle, aroyle, aryloxycarbonyle, hétérocyclylcarbonyle, hétérocyclyloxycarbonyle, hétérocyclylalcoxycarbonyle, hétéroaralcoxycarbonyle, hétéroaryloxycarbonyle ou hétéroaroyle ;
P^2 représente un hydrogène ;
R^2 représente des radicaux alkyle, aryle, cycloalkyle, cycloalkylalkyle ou aralkyle, radicaux éventuellement substitués par des radicaux alkyle, halogène, $-NO_2$, -CN, CF_3, $-OR^9$ ou $-SR^9$, où R^9 représente l'hydrogène ou des radicaux alkyle ;
R^3 représente des radicaux alkyle, alcényle, alcynyle, hydroxyalkyle, alcoxyalkyle, cycloalkyle, cycloalkylalkyle, hétérocyclyle, hétéroaryle, hétérocyclylalkyle, aryle, aralkyle ou hétéroaralkyle ; et
R^4 représente des radicaux alkyle, halogénoalkyle, alcényle, alcynyle, cycloalkyle, hétérocycloalkyle, hétéroaryle, aryle ou aralkyle et

où alkyle, seul ou dans une combinaison, est un radical hydrocarboné à chaîne linéaire ou ramifiée ayant 1 à 8 atomes de carbone ; alcényle, seul ou dans une combinaison, est un radical hydrocarboné à chaîne linéaire ou ramifiée ayant une ou plusieurs doubles liaisons et 2 à 8 atomes de carbone ; alcynyle, seul ou dans une

combinaison, est un radical hydrocarboné à chaîne linéaire ayant une ou plusieurs triples liaisons et 2 à 10 atomes de carbone ; cycloalkyle, seul ou dans une combinaison, est un cycle hydrocarboné contenant 3 à 8 atomes de carbone ; aryle, seul ou dans une combinaison, désigne un radical phényle ou naphtyle éventuellement substitué par des radicaux alkyle, alcoxy, halogène, hydroxy, amino, nitro, cyano ou halogénoalkyle ; hétérocyclyle ou hétérocycloalkyle désigne un hétérocycle monocyclique, bicyclique ou tricyclique, saturé ou partiellement insaturé, ayant un ou plusieurs hétéroatomes d'azote, d'oxygène ou de soufre, éventuellement substitué sur un ou plusieurs atomes de carbone par des radicaux halogène, alkyle, alcoxy ou oxo, ou sur un atome d'azote secondaire par des radicaux alkyle, aralcoxycarbonyle, alcanoyle, phényle ou phénylalkyle ou sur un atome d'azote tertiaire par un radical oxydo et hétéroaryle désigne un radical hétérocyclyle aromatique éventuellement substitué comme défini dans le cadre de la définition d'hétérocyclyle ;

où les radicaux aryle, quelle que soit leur position, peuvent éventuellement porter un ou plusieurs substituants choisis parmi alkyle, alcoxy, halogène, hydroxy, amino, nitro, cyano, halogénoalkyle ;

où les radicaux hétérocyclyle ou hétéroaryle peuvent éventuellement être substitués sur un ou plusieurs atomes de carbone par halogène, alkyle, alcoxy, oxo et/ou sur un atome d'azote secondaire par alkyle, aralcoxycarbonyle, alcanoyle, phényle ou phénylalkyle ou sur un atome d'azote tertiaire par oxydo et qui sont attachés par l'intermédiaire d'un atome de carbone ;

et ses sels, esters ou précurseurs de médicaments pharmaceutiquement acceptables.

6. Composé selon la revendication 5 dans lequel P^1 représente des radicaux alcoxycarbonyle, aralcoxycarbonyle, hétéroaralcoxycarbonyle, aroyle, hétéroaroyle, alcanoyle ou cycloalcanoyle ;

R^2 représente des radicaux alkyle, cycloalkylalkyle ou aralkyle, radicaux éventuellement substitués par des radicaux halogène, $-OR^9$ ou $-SR^9$, où R^9 représente l'hydrogène ou des radicaux alkyle ;
R^3 représente des radicaux alkyle, cycloalkyle ou cycloalkylalkyle et
R^4 représente des radicaux alkyle, aryle ou hétéroaryle.

7. Composé selon la revendication 6, dans lequel P^1 représente des radicaux 3-pyridylméthyloxycarbonyle, N-oxyde de 3-pyridylméthyloxycarbonyle, 4-pyridylméthyloxycarbonyle, N-oxyde de 4-pyridylméthyloxycarbonyle, 5-pyrimidylméthyloxycarbonyle, tert-butyloxycarbonyle, allyloxycarbonyle, 2-propyloxycarbonyle, benzyloxycarbonyle, cycloheptylcarbonyle, cyclohexylcarbonyle, cyclopentylcarbonyle, benzoyle, benzoyle substitué en 2, 4-pyridylcarbonyle, 2-méthylbenzoyle, 3-méthylbenzoyle, 4-méthylbenzoyle, 2-chlorobenzoyle, 2-éthylbenzoyle, 2,6-diméthylbenzoyle, 2,3-diméthylbenzoyle, 2,4-diméthylbenzoyle ou 2,5-diméthylbenzoyle ;

R^2 représente des radicaux benzyle, cyclohexylméthyle, 2-naphtylméthyle, para-fluorobenzyle, para-méthoxybenzyle, isobutyle ou n-butyle ;
R^3 représente des radicaux isobutyle, isoamyle, cyclohexyle, cyclohexylméthyle, n-butyle ou n-propyle ; et
R^4 représente des radicaux phényle, para-méthoxyphényle, para-cyanophényle, para-chlorophényle, para-hydroxyphényle, para-nitrophényle, para-fluorophényle, 2-naphtyle, 3-pyridyle, N-oxyde de 3-pyridyle, 4-pyridyle ou N-oxyde de 4-pyridyle.

8. Composé selon la revendication 5, dans lequel P^1 représente des radicaux hétérocyclylcarbonyle, hétérocyclyloxycarbonyle, hétérocyclylalcoxycarbonyle, hétéroaralcoxycarbonyle, hétéroaryloxycarbonyle ou hétéroaroyle ;

R^2 représente des radicaux alkyle, cycloalkylalkyle ou aralkyle, radicaux éventuellement substitués par des radicaux halogène, $-OR^9$ ou $-SR^9$, où R^9 représente l'hydrogène ou des radicaux alkyle ;
R^3 représente des radicaux alkyle, cycloalkyle ou cycloalkylalkyle et
R^4 représente des radicaux alkyle, aryle et hétéroaryle et

où hétérocyclyle ou hétérocycloalkyle désigne un hétérocycle à 5 ou 6 côtés ou un hétérocycle à 5 ou 6 côtés condensé à un cycle benzénique ayant un ou deux hétéroatomes d'azote, d'oxygène ou de soufre et hétéroaryle désigne un hétérocycle aromatique à 5 ou 6 côtés ou un hétérocycle aromatique à 5 ou 6 côtés condensé à un cycle benzénique ayant un ou deux hétéroatomes d'azote, d'oxygène ou de soufre.

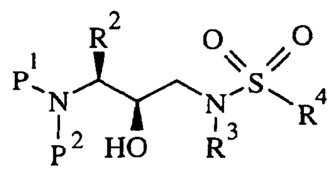
9. Composé selon la revendication 8, dans lequel P^1 représente des radicaux hétérocyclylcarbonyle, hétérocyclyloxycarbonyle, hétérocyclylalcoxycarbonyle, hétéroaralcoxycarbonyle, hétéroaryloxycarbonyle ou hétéroaroyle ;

R^2 représente des radicaux benzyle, cyclohexylméthyle, 2-naphtylméthyle, para-fluorobenzyle, para-méthoxybenzyle, isobutyle ou n-butyle ;

R^3 représente des radicaux isobutyle, isoamyle, cyclohexyle, cyclohexylméthyle, n-butyle ou n-propyle ; et

où hétérocyclyle ou hétérocycloalkyle désigne un hétérocycle à 5 ou 6 côtés ayant un ou deux hétéroatomes d'azote, d'oxygène ou de soufre et hétéroaryle désigne un hétérocycle aromatique à 5 ou 6 côtés ayant un ou deux hétéroatomes d'azote, d'oxygène ou de soufre.

10. Composé inhibant une protéase de rétrovirus selon la revendication 1, ayant pour formule



dans laquelle :

P^1 représente des radicaux alcoxycarbonyle, aralcoxycarbonyle, alkylcarbonyle, cycloalkylcarbonyle, cycloalkylalcoxycarbonyle, cycloalkylalcanoyle, alcanolyle, aralcanoyle, aroyle, aryloxycarbonyle, aryloxycarbonylalkyle, aryloxyalcanoyle, hétérocyclylcarbonyle, hétérocyclyloxycarbonyle, hétérocyclylalcanoyle, hétérocyclylalcoxycarbonyle, hétéroaralcanoyle, hétéroaralcoxycarbonyle, hétéroaryloxycarbonyle, hétéroaroyle, alkyle, alcényle, cycloalkyle, aryle, aralkyle, aryloxyalkyle, hétéroaryloxyalkyle, hydroxyalkyle, aminocarbonyle, aminoalcanoyle et aminocarbonyle mono- et disubstitué et aminoalcanoyle mono- et disubstitué, les substituants étant choisis parmi les radicaux alkyle, aryle, aralkyle, cycloalkyle, cycloalkylalkyle, hétéroaryle, hétéroaralkyle, hétérocycloalkyle, hétérocycloalkylalkyle, ou, quand ledit radical aminoalcanoyle est disubstitué, lesdits substituants forment, avec l'atome d'azote auquel ils sont rattachés, un radical hétérocycloalkyle ou hétéroaryle ;
P^2 représente l'hydrogène ;
R^2 représente des radicaux alkyle, aryle, cycloalkyle, cycloalkylalkyle et aralkyle, radicaux éventuellement substitués par un groupe choisi parmi les radicaux alkyle et halogène, $-NO_2$, $-C{\equiv}N$, CF_3, $-OR^9$, $-SR^9$, où R^9 représente l'hydrogène et des radicaux alkyle ;
R^3 représente l'hydrogène, des radicaux alkyle, halogénoalkyle, alcényle, alcynyle, hydroxyalkyle, alcoxyalkyle, cycloalkyle, cycloalkylalkyle, hétérocycloalkyle, hétéroaryle, hétérocycloalkylalkyle, aryle, aralkyle, hétéroaralkyle, aminoalkyle et aminoalkyle mono- et disubstitués, lesdits substituants étant choisis parmi les radicaux alkyle, aryle, aralkyle, cycloalkyle, cycloalkylalkyle, hétéroaryle, hétéroaralkyle, hétérocycloalkyle et hétérocycloalkylalkyle, ou, dans le cas d'un radical aminoalkyle disubstitué, lesdits substituants formant, avec l'atome d'azote auquel ils sont rattachés, un radical hétérocycloalkyle ou un radical hétéroaryle ; et
R^4 représente les radicaux tels que définis pour R^3, exception faite de l'hydrogène ;

où les radicaux aryle, quelle que soit leur position, peuvent éventuellement porter un ou plusieurs substituants choisis parmi alkyle, alcoxy, halogène, hydroxy, amino, nitro, cyano, halogénoalkyle ;
où les radicaux hétérocyclyle ou hétéroaryle peuvent éventuellement être substitués sur un ou plusieurs atomes de carbone par halogène, alkyle, alcoxy, oxo et/ou sur un atome d'azote secondaire par alkyle, aralcoxycarbonyle, alcanoyle, phényle ou phénylalkyle ou sur un atome d'azote tertiaire par oxydo et qui sont attachés par l'intermédiaire d'un atome de carbone ;
et ses sels, esters ou précurseurs de médicaments pharmaceutiquement acceptables.

11. Composé selon la revendication 10, dans lequel

R^2 représente des radicaux cycloalkylalkyle, aralkyle, alkyle, benzyle, cyclohexylméthyle, 2-naphtylméthyle, para-fluorobenzyle, para-méthoxybenzyle, isobutyle ou n-butyle ;
R^3 représente des radicaux alkyle, cycloalkyle, cycloalkylalkyle, isobutyle, isoamyle, cyclohexyle, cyclohexylméthyle, n-butyle ou n-propyle ; et
R^4 représente des radicaux aryle, alkyle, aryle, aryle para-substitué, hétéroaryle, phényle, para-méthoxyphényle, para-cyanophényle, para-chlorophényle, para-hydroxyphényle, para-nitrophényle, para-fluorophényle, 2-naphtyle, 3-pyridyle, N-oxyde de 3-pyridyle, 4-pyridyle ou N-oxyde de 4-pyridyle.

12. Composition pharmaceutique comprenant un composé selon une quelconque des revendications 1 à 11 et un support pharmaceutiquement acceptable.

13. Utilisation d'une composition selon la revendication 12, pour la préparation d'un médicament pour l'inhibition d'une protéase de rétrovirus.

14. Utilisation selon la revendication 13, dans laquelle la protéase de rétrovirus est une protéase de VIH.

15. Utilisation d'une composition selon la revendication 12, pour la préparation d'un médicament pour le traitement d'une infection par un rétrovirus.

16. Utilisation selon la revendication 15, dans laquelle l'infection par un rétrovirus est une infection par un VIH.

17. Utilisation d'une composition selon la revendication 12, pour la préparation d'un médicament pour le traitement du SIDA.